Bioavailability

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Remediation Innovative Technology Seminar

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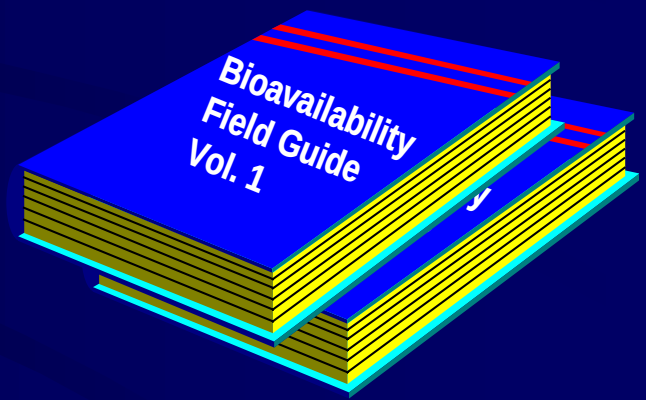
Objectives of This Presentation

- Discuss the bioavailability field guide goals, audience, and material
- Present an overview of bioavailability
- Describe how bioavailability can support risk assessments and decisions

The Bioavailability Field Guide

- Three levels of audience
  - Upper Management
  - Remedial Project Manager (RPM)
  - Risk Assessor
- Two volumes
  - The RPM Bioavailability Manual
  - The Risk Assessor Bioavailability Technical Reference



The Bioavailability Field Guide

- Is available in draft on the NAVFAC intranet
  - www.155.252.204.90
- Please provide comments to:
  - Teresa Bernhard at tsbernhard@efawest.navfac.navy.mil

Regulatory Policies: EPA

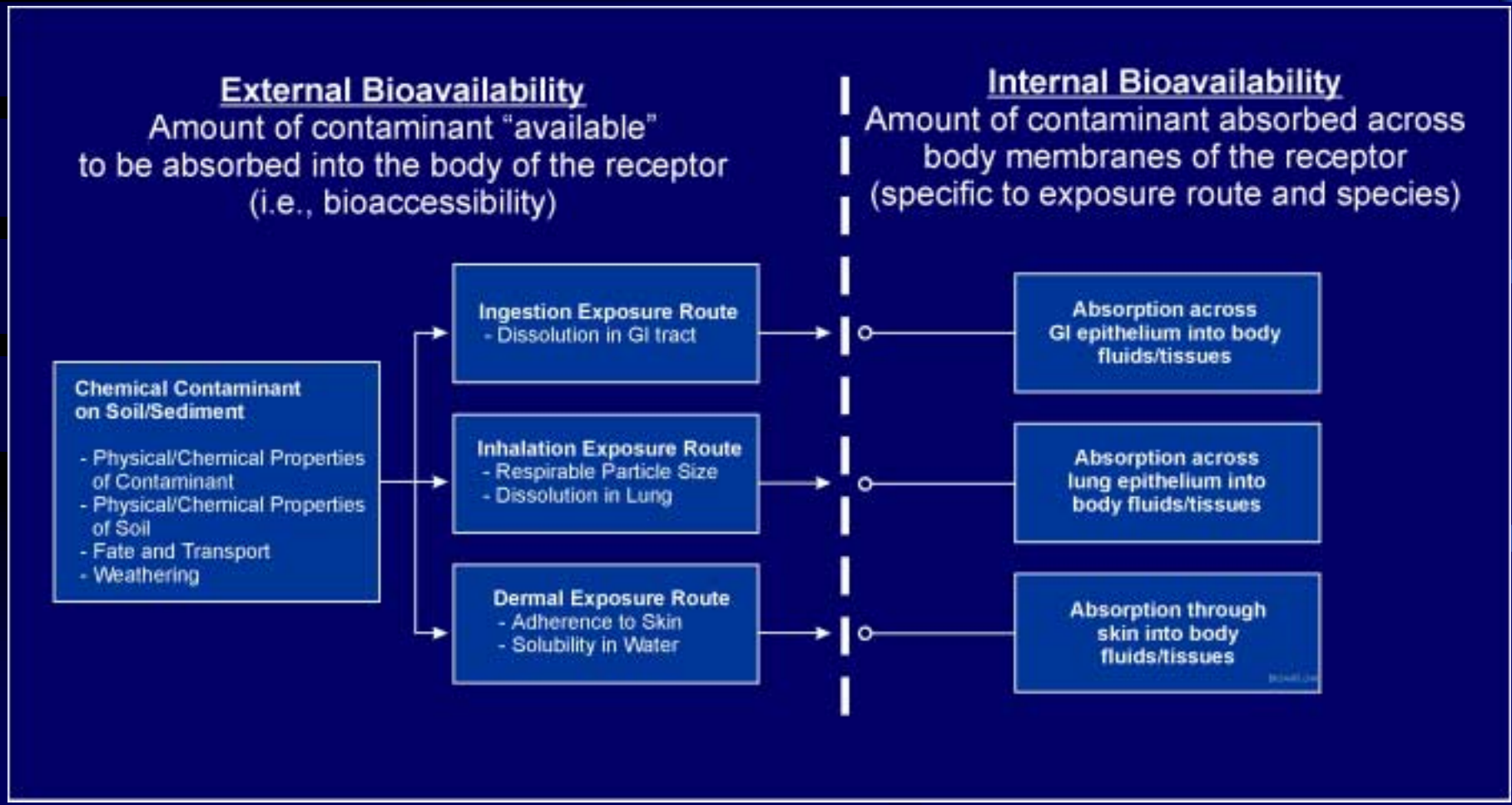
"If the medium of exposure at the site…differs from the medium of exposure assumed by the toxicity value…an absorption adjustment may...be appropriate."

Risk Assessment Guidance for Superfund (RAGS), 1989

Bioavailability is:

- The extent to which a substance can be absorbed by a living organism by active (biological) or passive (physical or chemical) processes. A substance is bioavailable if it is in both a chemical form and a location that allows it to move through an exchange boundary or surface coating (i.e., skin, gut lining, lung lining, cell membrane, or gill epithelium) of an organism and, in so doing, cause a physiological or toxicological response.

Key Concepts of External and Internal Bioavailability



Two Important Terms:

- **Absolute bioavailability:**

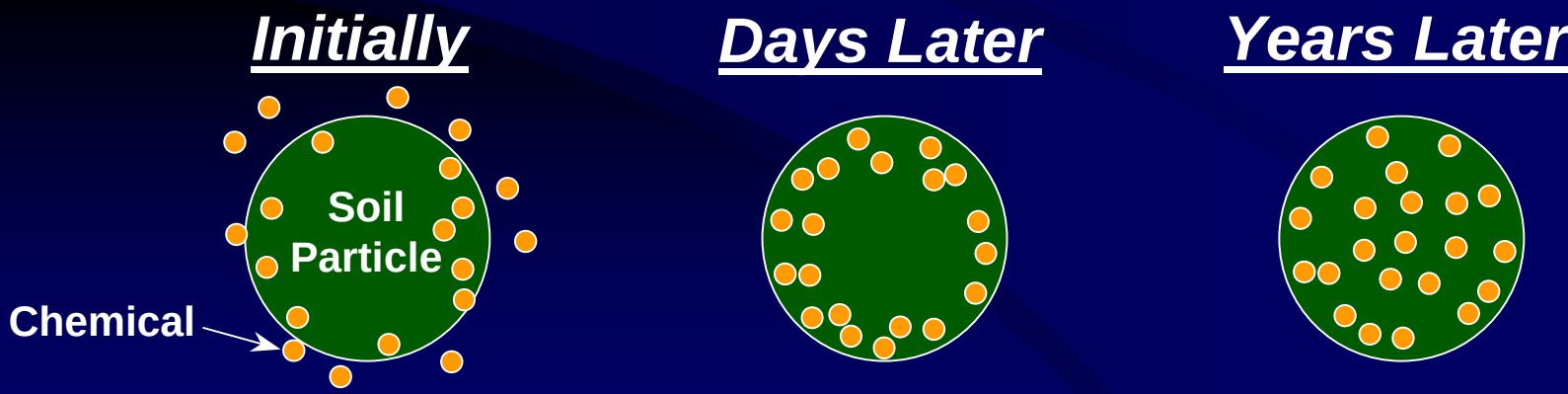
  Fraction of intake reaching the blood

- **Relative bioavailability:**

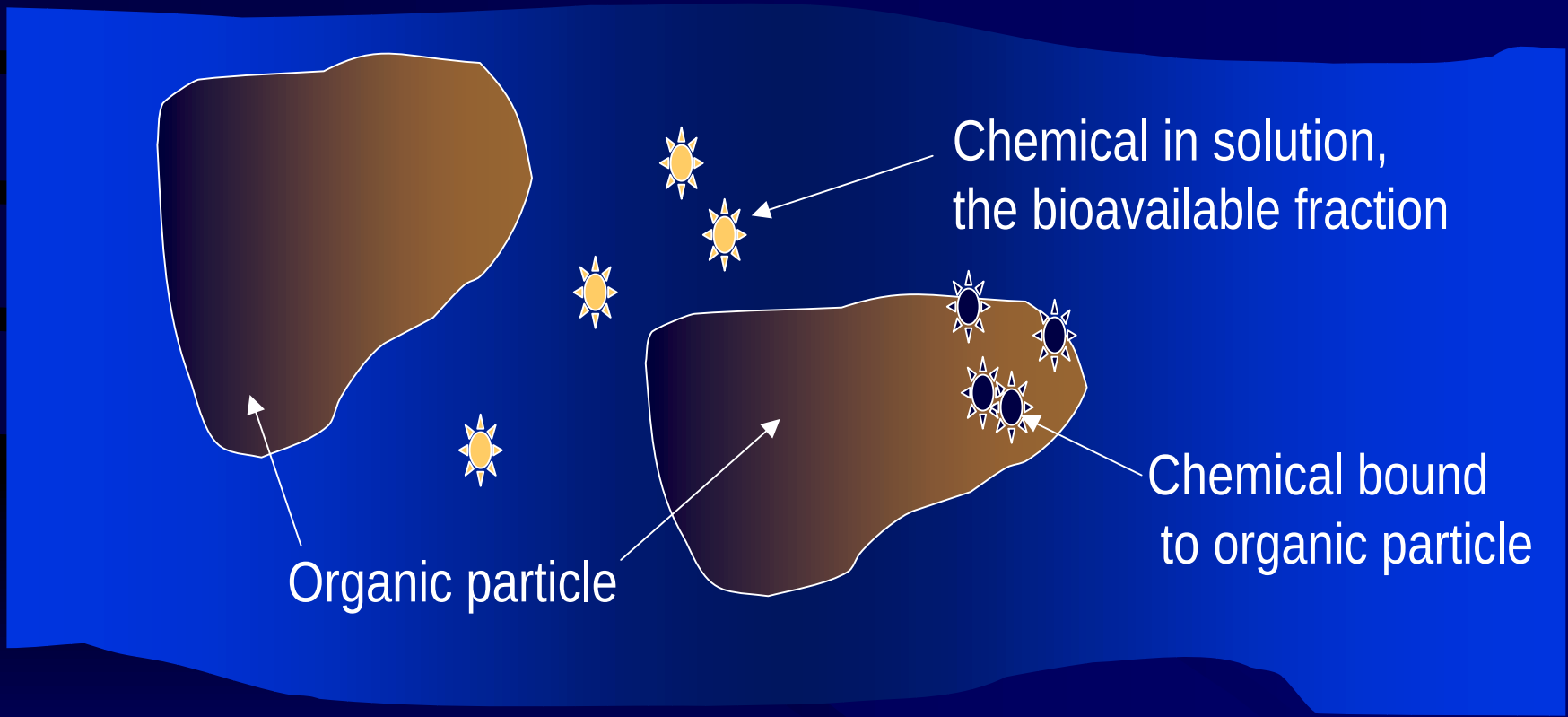
  Difference in absorption between site exposure medium and dosing medium from the toxicity study

Why are Chemicals Less Bioavailable in Soil?

- Insoluble or poorly soluble materials generally are less well absorbed than soluble materials
- Substances tend to sequester to soil matrices over time. These sequestered substances are less soluble and less bioavailable



Chemical Physically Bound to a Substance = Less Soluble



How Can Bioavailability be Used in Risk Assessments?

Toxicity x Exposure = Risk

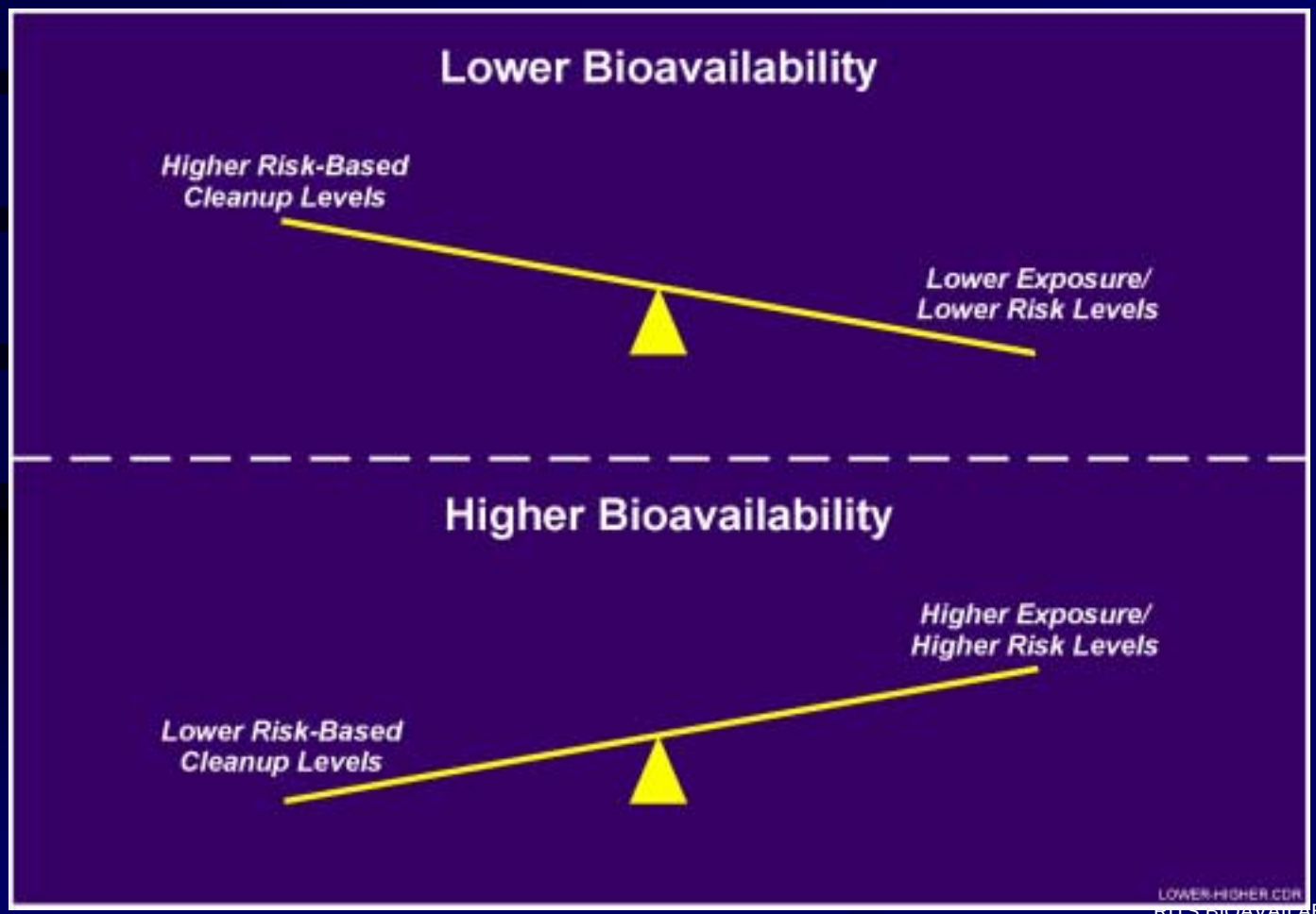
Bioavailability data can be used to adjust the exposure calculations to more accurately reflect the relative absorption factor

What Are the Benefits of Considering Bioavailability in Studies?

A relative absorption factor of 1 is an unstated assumption in most risk assessments. Bioavailability studies:

- May increase certainty regarding remedial and risk decisions
- Assist in the evaluation of remedial alternatives
- Potentially reduce conservativeness inherent in risk assessments, thereby changing cleanup goals and reducing cost

The Benefits of Considering Bioavailability



When Do We Consider Bioavailability?

- When an evaluation of site data or history implies that the bioavailability of chemicals at a site may affect the resulting site-specific exposures
- When costs of site remediation are high and certainty is low
- When the feasibility of a remedy is unclear
- When the risk of the remedy may outweigh the risk from the site for the chemicals
- When long-term management of the site is costly and is based on the risk assessment

Navy Ecological Risk Assessment (ERA) Tiered Approach

RPM Input and Risk Management Consideration[3]

Step 8: Risk Management

Tier 1. Screening Risk Assessment (SRA): Identify pathways and compare exposure point concentrations to benchmarks.

Step 1: Site Visit; Pathway Identification/Problem Formulation; Toxicity Evaluation

Step 2: Exposure Estimate; Risk Calculation (SMDP) [1]

Proceed to Exit Criteria for SRA

Exit Criteria for the Screening Risk Assessment: Decision for exiting or continuing the ERA.

Tier 2. Baseline Ecological Risk Assessment (BERA): Detailed assessment of exposure and hazard to "assessment endpoints" (ecological qualities to be protected). Develop site-specific values that are protective of the environment.

Step 3a: Refinement of Conservative Exposure Assumptions[2] (SRA)---- **Proceed to Exit Criteria for Step 3a**

Step 3b: Problem Formulation - Toxicity Evaluation; Assessment Endpoints; Conceptual Model; Risk Hypothesis (SMDP)

Step 4: Study Design/DQO - Lines of Evidence; Measurement Endpoints; Work Plan and Sampling & Analysis Plan (SMDP)

Step 5: Verification of Field Sampling Design (SMDP)

Step 6: Site Investigation and Data Analysis (SMDP)

Step 7: Risk Characterization **Proceed to Exit Criteria for BERA**

Use Bioavailability Here

Exit Criteria Step 3a Refinement

1) If re-evaluation of the conservative exposure assumptions (SRA) support an acceptable risk determination, then the site exits the ERA process.

2) If re-evaluation of the conservative exposure assumptions (SRA) do not support an acceptable risk determination, then the site continues in the BERA process. **Proceed to Step 3b**.

Exit Criteria BERA

1) If the site poses acceptable risk then no further evaluation and no remediation from an ecological perspective is warranted.

2) If the site poses unacceptable ecological risk and additional evaluation in the form of remedy development and evaluation is appropriate, proceed to third tier.

Tier 3. Evaluation of Remedial Alternative (RAGS C)

a. Develop site-specific, risk-based cleanup values.

b. Qualitatively evaluate risk posed to the environment by implementation of each alternative (short-term) impact and estimate risk reduction provided by each (long-term) impact; provide quantitative evaluation where appropriate. Weigh alternative using the remaining CERCLA 9 Evaluation Criteria. Plan for monitoring and site closeout.

Notes: 1) See EPA's 8-Step ERA Process for requirements for each Scientific Management Decision Point (SMDP).

2) Refinement includes but is not limited to background, bioavailability, and detection frequency.

3) Risk Management is incorporated throughout the tiered approach.

When Should We "Pass" on the Bioavailability Question?

- When dose response data from studies for the chemical of concern in the matrix of concern already exist
- When the risk assessment, uncertainty analysis, or sensitivity analysis implies that bioavailability is not a driving force in the risk
- When the cost of site remediation is minimal relative to the cost of a bioavailability study
- When existing chemical or toxicological literature and data may qualitatively support alternative decisions
- When there are more than 3 COPCs

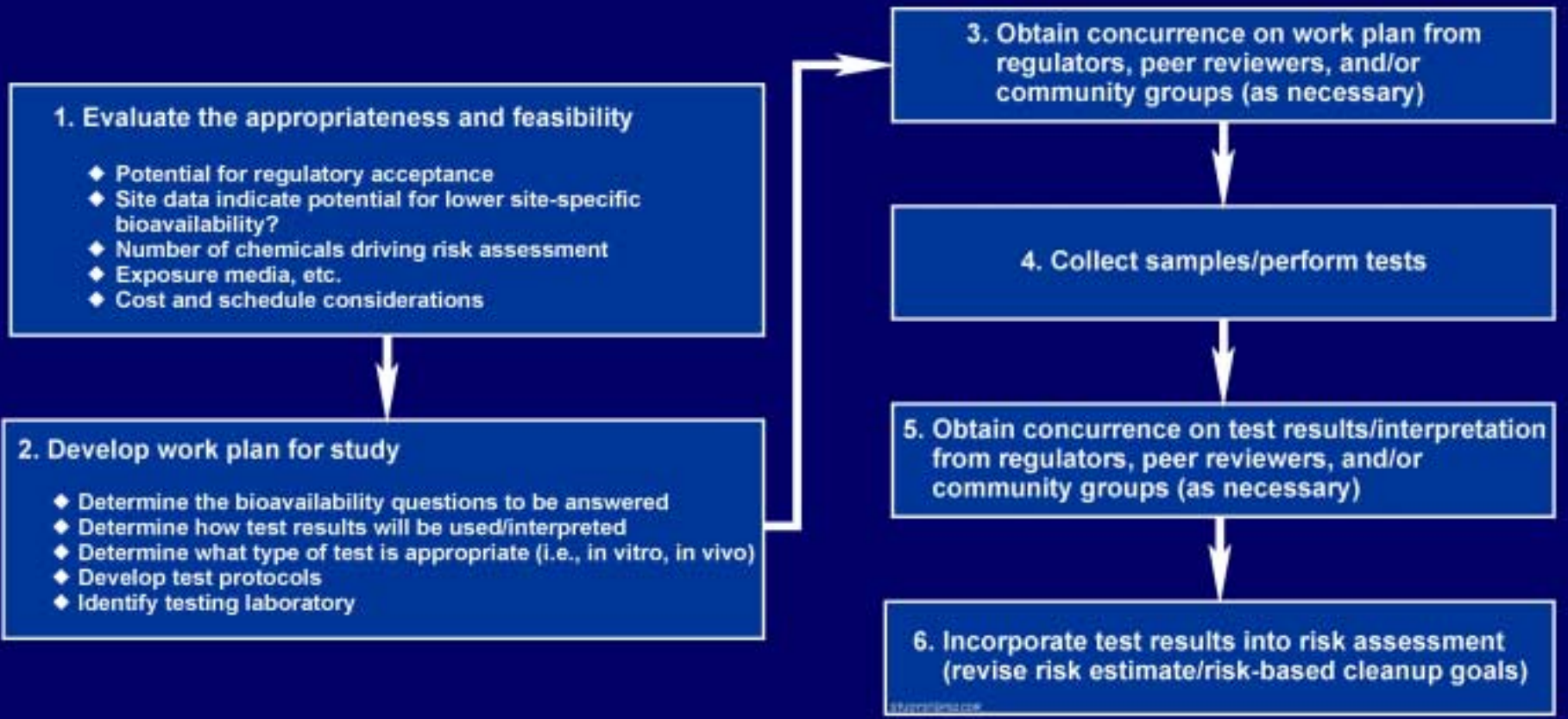
What Should an RPM Know About Bioavailability Studies?

- Plan ahead. In the risk assessment workplan, plan for and suggest bioavailability adjustments.
- Design bioavailability studies and plan the use of the study data in conjunction with regulators.
- Get agreement up front on how the data is to be taken and used.
- Cite data and decisions from other sites.

What Should an RPM Know About Bioavailability Studies? (cont.)

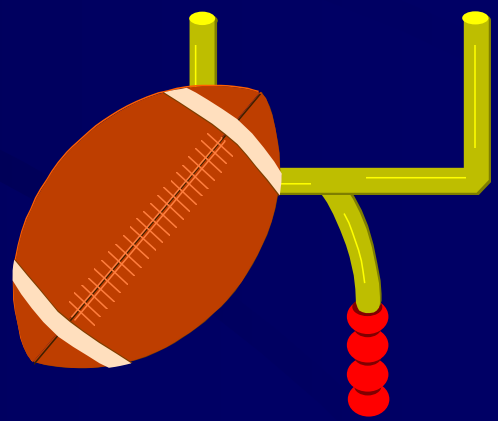
- Get outside sources (such as peer review) to review the study design and the final risk assessment.
- Ensure adequate technical support from toxicologists, experts in bioavailability and study design, and risk assessors.
- Plan for the cost up front.
- Plan for time.

Steps for a Bioavailability Study



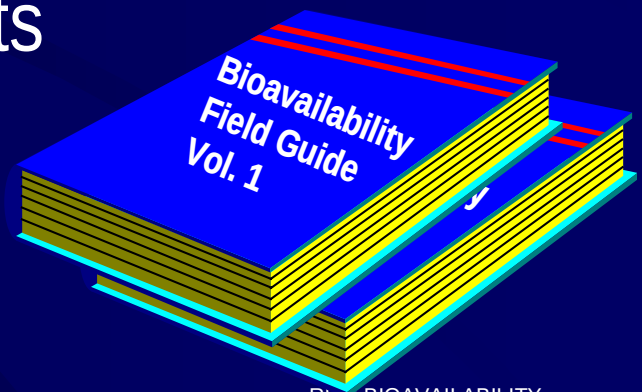
The Bioavailability Field Guide Goal

- To supply Navy management, project managers, and risk assessors with information about the utilization of bioavailability in risk assessment and risk management and also about how bioavailability might be used in site assessments



The Bioavailability Field Guide

- Has decision flowcharts to guide participants through the important steps of bioavailability and the utilization of bioavailability in risk assessments
- Has extensive support literature to assist risk assessors in determining the usefulness of bioavailability in risk assessments



Why Consider Bioavailability in Risk Assessment?

- Is bioavailability currently considered?
- What are the advantages of collecting site-specific data?
- How are such studies planned and conducted?
- How are results used?
- What resources are available?

Outline

- Definitions and review of risk assessment procedures
- Regulatory policies and precedents
- Geochemical considerations
- Methods review
- Case studies
- Ecological risk assessment applications
- Conclusions: Role of RPM, resources, Navy policy recommendations

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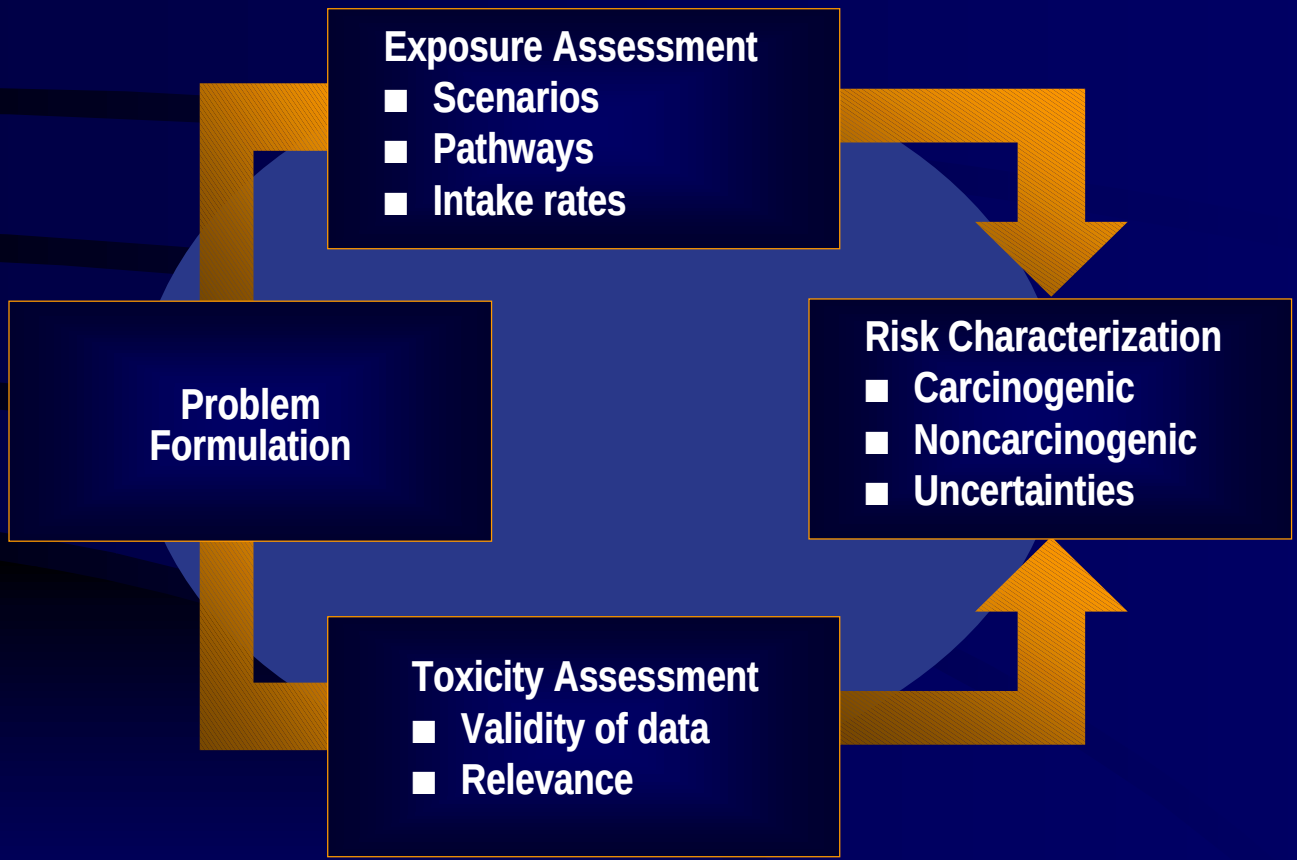
- Definitions and review of risk assessment procedures

Absolute Bioavailability

Fraction of intake reaching the central compartment; i.e., blood

Why is Bioavailability Relevant to Risk Assessment?



Consideration of Bioavailability in Risk Assessment

Toxicity x **Exposure** = **Risk**

- Different Species
- Sensitive Receptors

- Different Routes
- Different Media
- Variation within Medium

Basis for Oral Toxicity Values for Selected Metals

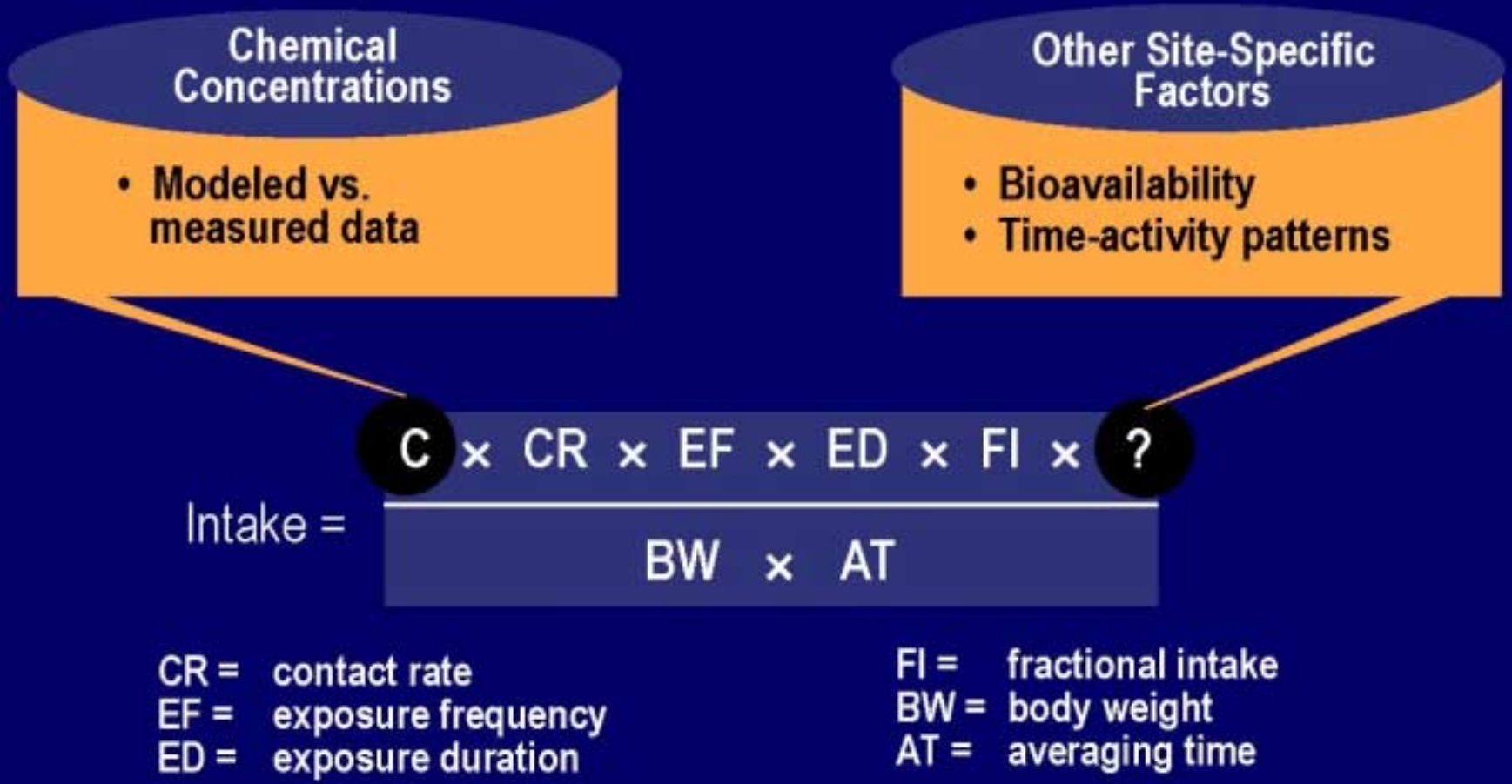
Chemical	Toxicity Value		Toxicity Endpoint	Species, Study Type	Exposure Medium/ Chemical Form
Arsenic					
Inorganic	RfD	$3x10^{-4}$ mg/kg-day	Hyperpigmentation, keratosis, possible vascular complications	Human, chronic oral	Drinking water, food/ dissolved arsenic
	CSF	$1.5\ (mg/kg\text{-}day)^{-1}$	Skin cancer	Human, chronic oral	Drinking water/ dissolved arsenic
Cadmium	RfD–water	$5x10^{-4}$ mg/kg/day	Significant proteinuria	Human, number of chronic studies	Water, food
	RfD–food	$1x10^{-3}$ mg/kg-day			
Chromium					
Chromium(III) insoluble salts	RfD	1.5 mg/kg-day	NOAEL	Rat, chronic feeding study	Diet/Cr_2O_3
Chromium(VI)	RfD	$3x10^{-3}$ mg/kg-day	NOAEL	Rat, 1-year drinking study	Water/K_2CrO_4
Mercury					
Mercuric chloride	RfD	$3x10^{-4}$ mg/kg-day	Autoimmune effects	Rat, subchronic feeding and subcutaneous studies	Gavage, subcutaneous injection/mercuric chloride
Nickel					
Soluble salts	RID	$2x10^{-2}$ mg/kg-day	Decreased body and organ weights	Rat, chronic oral	Diet/nickel sulfate

Relative Bioavailability

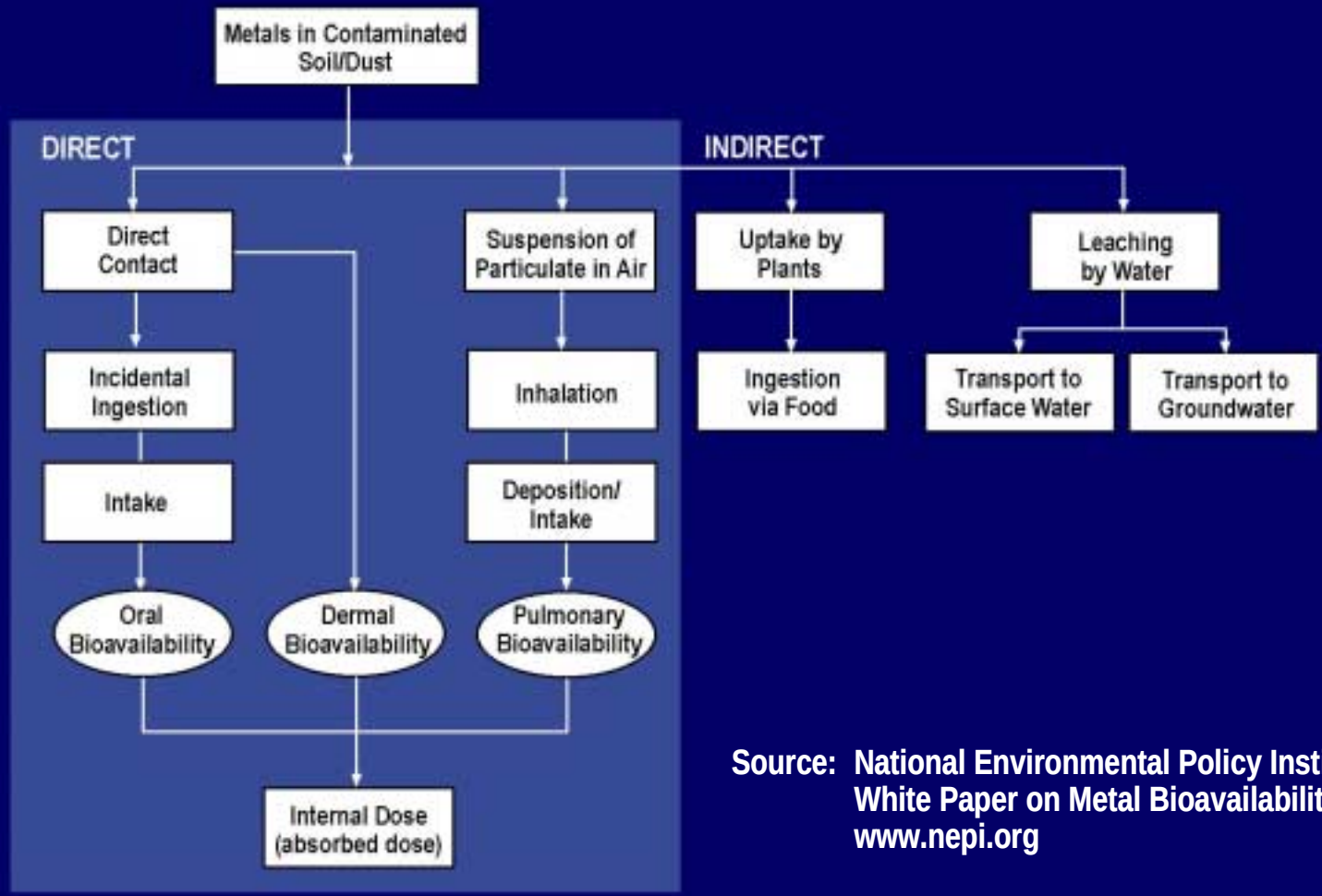
$$RAF = \frac{\text{Absorption for exposure medium of concern}}{\text{Absorption for medium used in toxicity study}}$$

RAF = Relative absorption factor

Exposure Assessment



Exposure Pathways for Metals in Soil/Dust: Direct Contact vs. Indirect Pathways



Source: National Environmental Policy Institute White Paper on Metal Bioavailability, www.nepi.org

Identify Sources of Uncertainty

Exposure Scenario

Exposure Pathways

- Inhalation of particulates and vapors
- Ingestion of soil
- Ingestion of homegrown produce
- Dermal absorption

Exposure Parameters

- Soil ingestion/contact rate
- Exposure frequency
- Exposure duration
- Bioavailability
- Body weight
- Relationship between soil and dust concentrations

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- Regulatory policies and precedents

U.S. Regulatory Frameworks

- CERCLA
- RCRA
- State hazardous waste site laws
- State voluntary cleanup laws
- Brownfield laws

Regulatory Policies: EPA

"If the medium of exposure [at] the site…differs from the medium of exposure assumed by the toxicity value…an absorption adjustment may…be appropriate."

Risk Assessment Guidance for Superfund (RAGS), 1989

EPA Recommends an RAF:

"[to] adjust a food or soil ingestion exposure estimate to match a RfD – or slope factor based on…drinking water…"

Risk Assessment Guidance for Superfund (RAGS), 1989

EPA Lead Exposure Models

- Default assumptions for absolute bioavailability, water and food = 50%; soil = 30%
- So, default soil lead RAF = 0.6 (i.e., 30% divided by 50%)
- Site-specific data acceptable

U.S. EPA, 1994, 1996

State Policies

State	RAF/Policy
Michigan	• Default = 0.5 (inorganics and nonvolatiles)
Washington	• Default for arsenic = 0.4, site-specific data considered
Massachusetts	• Selected defaults <1, site-specific data considered (in vitro cyanide studies)
New Jersey	• Site-specific data considered (animal studies)
Florida	• Site-specific data considered
West Virginia	• Same defaults <1, site-specific data considered

Precedents for Metals: EPA-Administered Sites

Region	Site	Metal/RAF/Basis
VIII	Butte, MT	Pb/0.24/animal
VIII	Anaconda, MT	As/0.18/animal
VIII	Salt Lake City, UT	Pb/0.38–0.60/animal
III	Palmerton, PA	As/0.44/animal
IV	Oak Ridge, TN	Hg/0.10/speciation and in vitro
IX	Carson River, NV	Hg/0.3/speciation
X	Tacoma, WA	As/0.8/animal

Precedents for Metals: State/Provincial Sites

State	Site	Metal/RAF/Basis
Oklahoma	Bartlesville	Pb/0.4/animal Cd/0.33/animal As/0.25/in vitro
Michigan	Lansing (park)	As/0.10/speciation and in vitro
California	Los Gatos (park)	Hg/0.3/speciation and in vitro
British Columbia	Wells	As/0.3/in vitro
California	Sacramento (rail yard)	As/0/animal
Illinois	Chicago (steel mill)	Pb/0.48/in vitro Mn/0.23/in vitro

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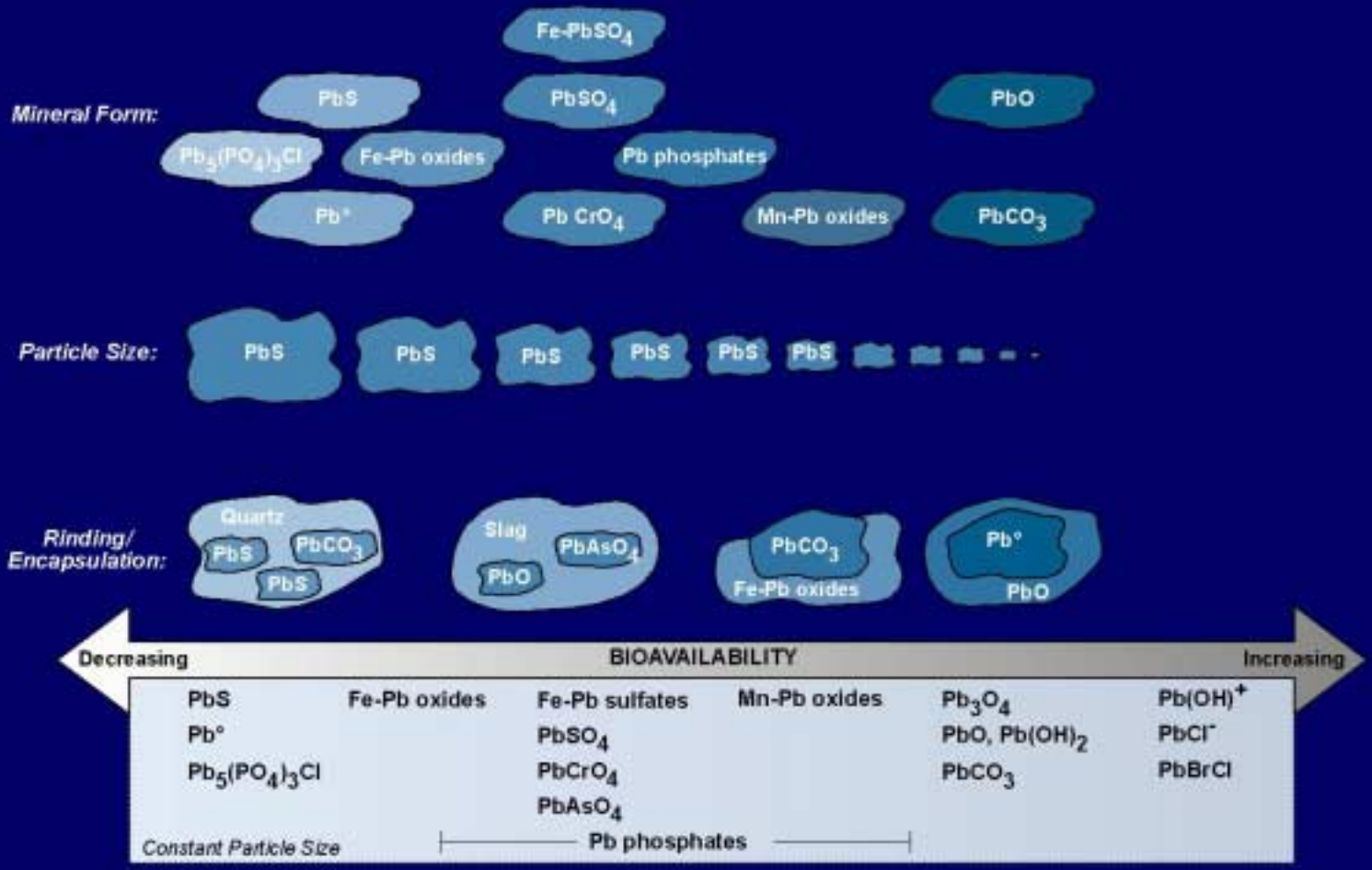
- Geochemical considerations

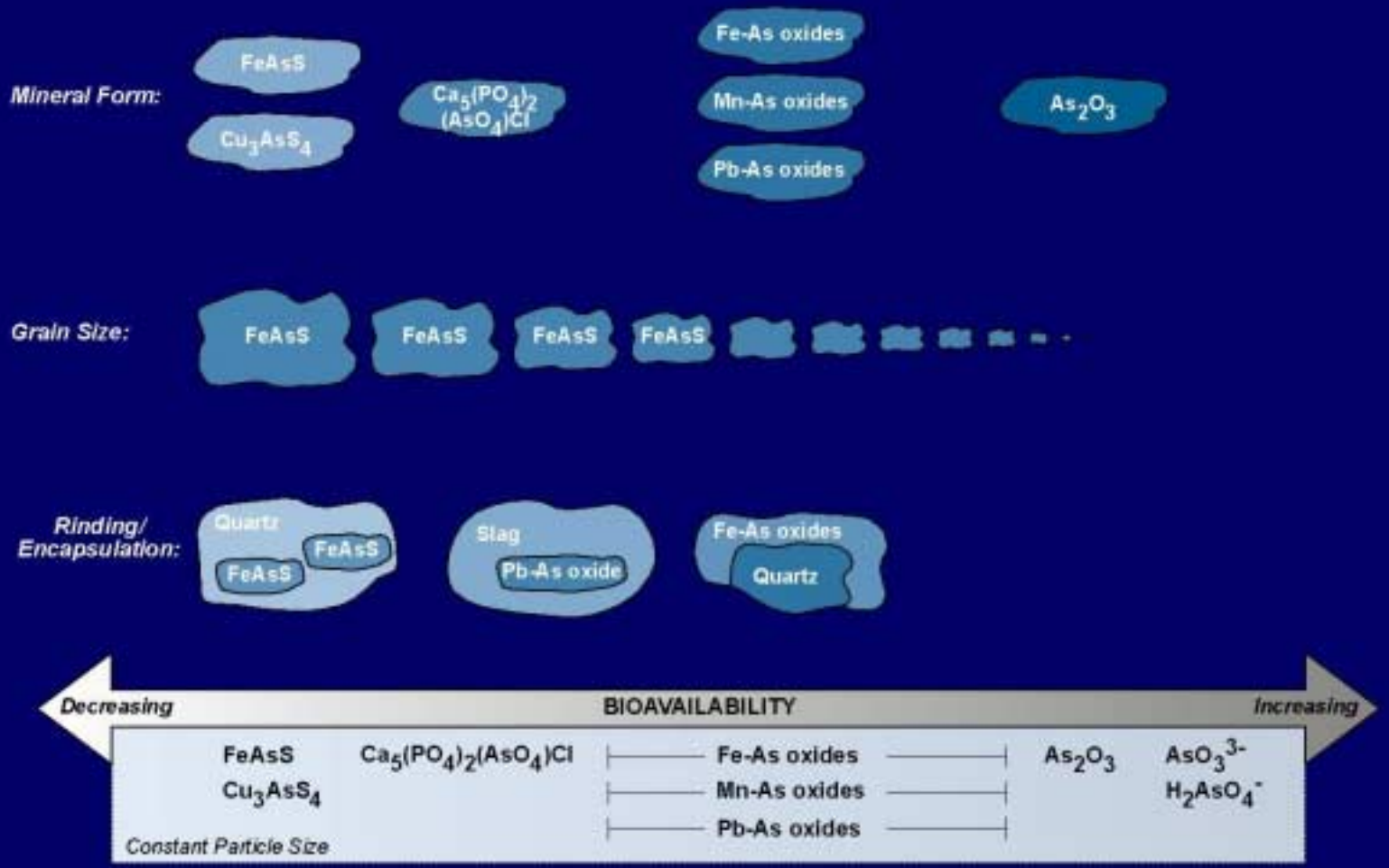
Why Are Chemicals in Soil Less Bioavailable?

Insoluble or poorly soluble materials are generally less well absorbed than soluble materials.

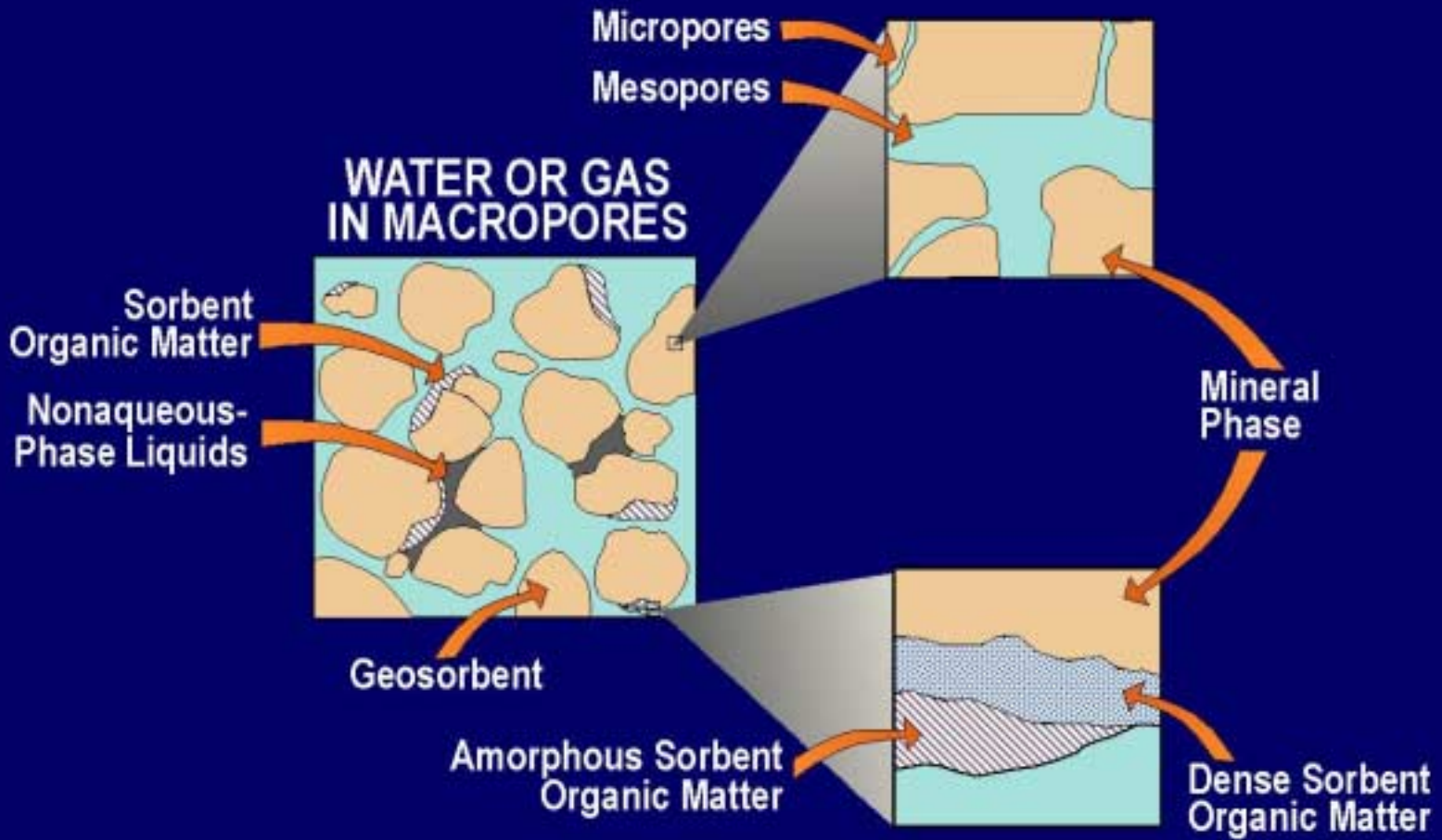
Influence of Lead Species, Particle Size, and Morphology on Lead Bioavailability



Influence of Arsenic Species, Particle Size, and Morphology on Arsenic Bioavailability



Sequestration Mechanisms for Hydrophobic Organic Compounds in Soil



Adapted from Luthy et al., 1997. Sequestration of Hydrophobic Organic Contaminants by Geosorbents. Environ. Sci. Technol. 31(12):3341–3357.

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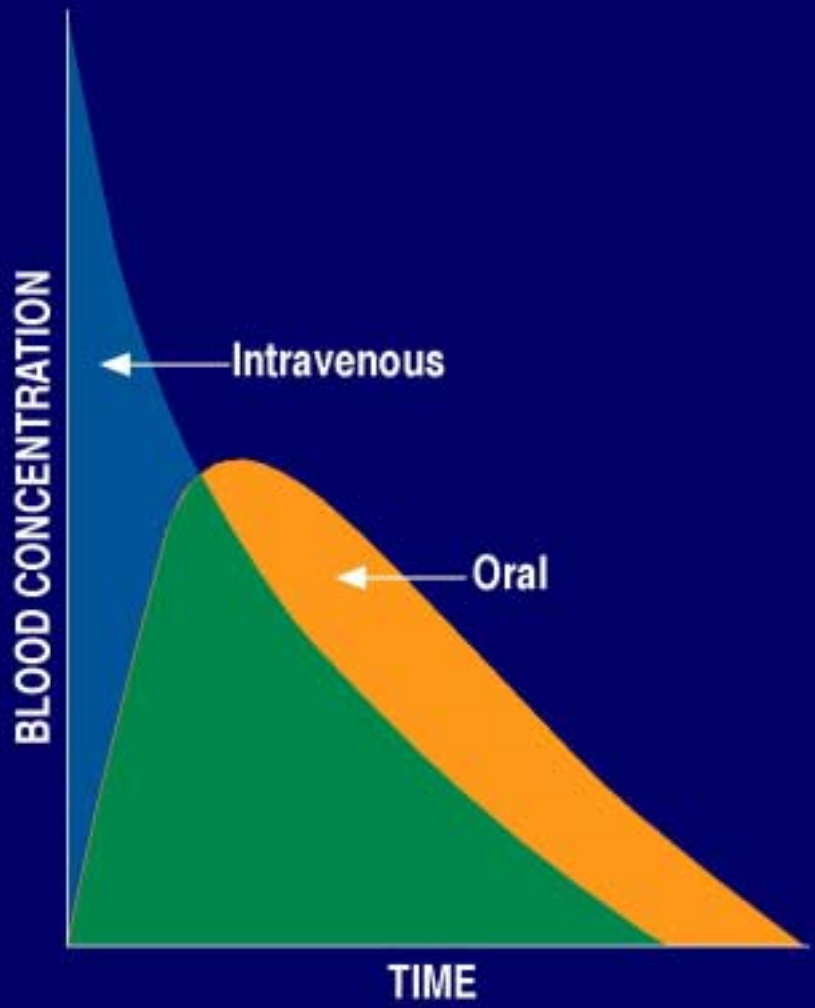
What Kind of Bioavailability Data Are Needed to Support an RAF?

- Literature data
- Site-specific data
  - Mineralogy/speciation
  - In vitro test systems
  - Laboratory animal studies

In Vivo Methods of Measuring Bioavailability

- Blood concentration over time (area under the curve, or AUC)
- Absorbed fraction in urine and/or tissues
- Comparison of tissue concentrations
- Unabsorbed fraction in feces

Comparison of AUCs for Blood Concentrations



Limitation:

Most accurate when chemical is rapidly excreted.

Unabsorbed Fraction in Feces

$$\text{Absorption (\%)} = \frac{\text{Total oral dose - amount in feces}}{\text{Total oral dose}} \times 100$$

Confounding factors:

- Biliary excretion, absorption will be underestimated (test by measuring fecal excretion after intravenous dose).
- Retention in intestinal mucosa, absorption will be overestimated.

Comparison of Urinary Excretion

$$\text{Arsenic Bioavailability} = \frac{\left(\frac{As_{urinary}}{As_{dose}}\right)_{oral}}{\left(\frac{As_{urinary}}{As_{dose}}\right)_{IV}}$$

Limitation:

Chemical must be excreted primarily in urine.

Comparison of Tissue Concentrations

Relative absorption factor (RAF) =

$$\frac{\text{[Lead concentration in bone] oral soil lead}}{\text{[Lead concentration in bone] oral soluble lead}}$$

Limitation:

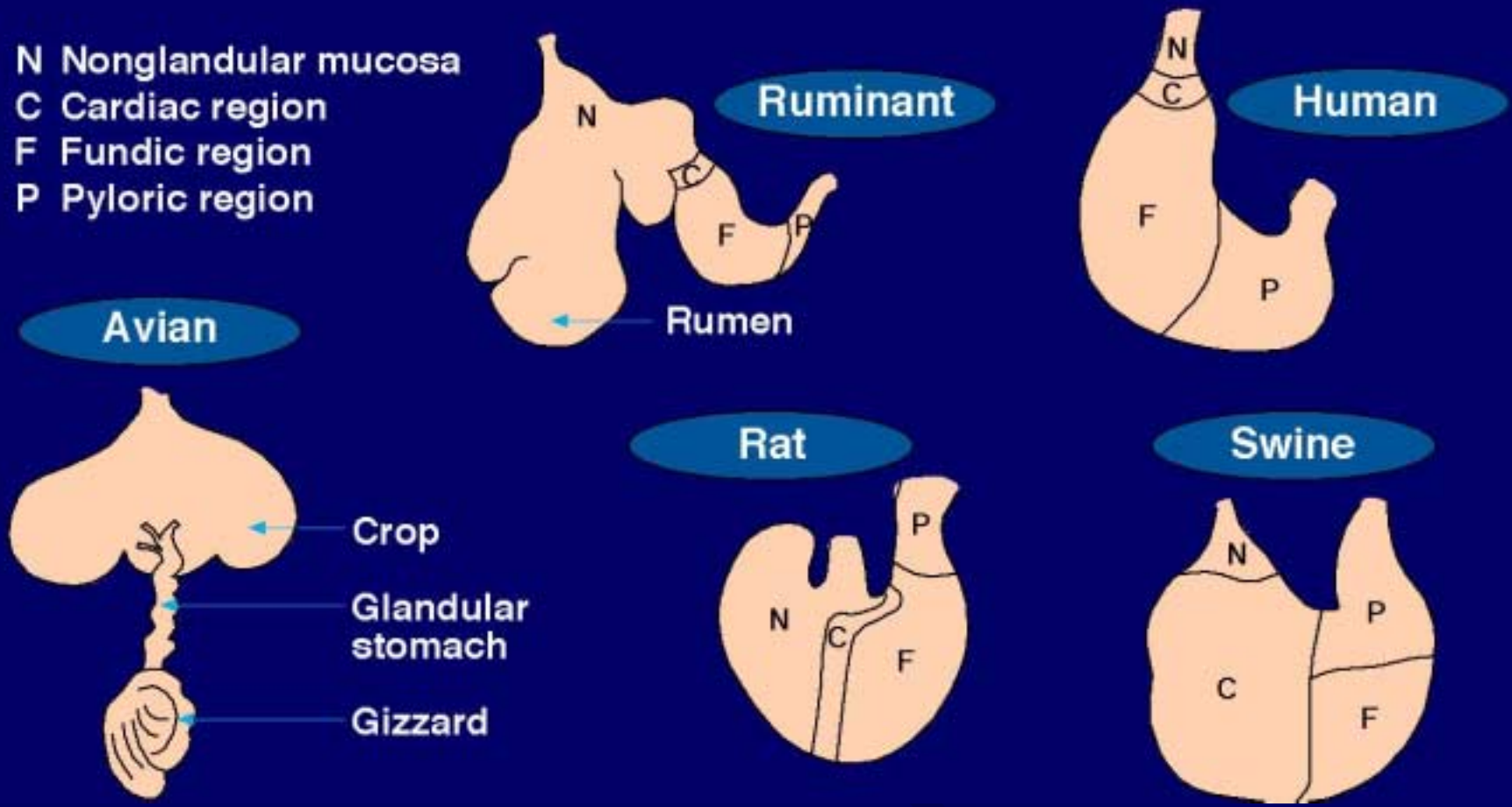
RAF only, not absolute bioavailability.

Design Considerations for In Vivo Studies in Animals

Select Animal Model

- Chemical behavior in animal vs. humans
- Age
- Sex
- Nutritional status and diet
- Cost and availability of animals

Variations in Gastric Anatomy



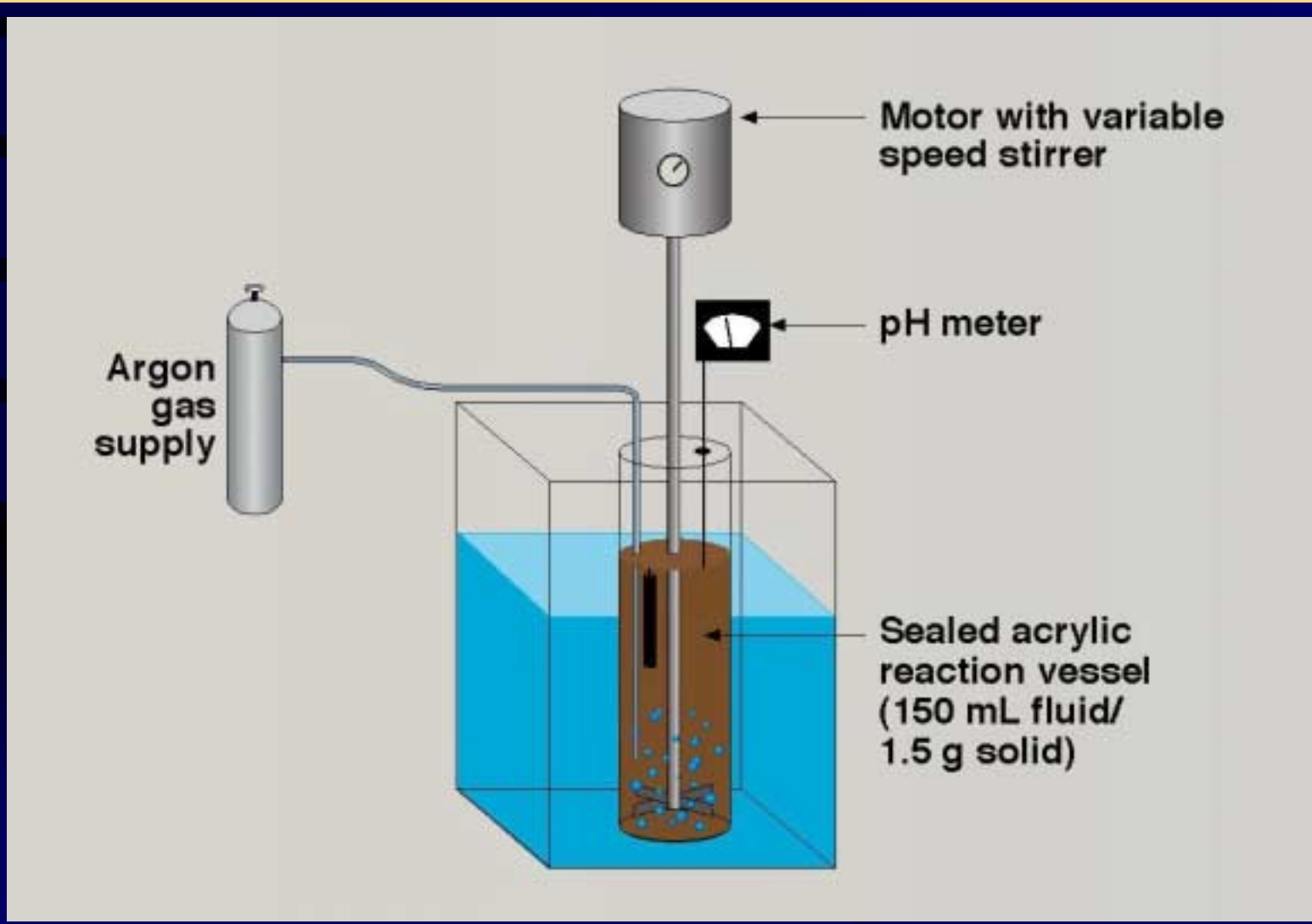
Design Considerations for In Vivo Studies in Animals (continued)

Specify Study Design (protocol)

- Animal model
- Test substance (e.g., soil particle size range)
- Dose levels
- Positive controls (e.g., intravenous and oral administration of compound in solution)
- Single dose vs. repeated dose
- Number of animals per group
- Animals fasted or fed
- Samples to collect (e.g. urine, feces, blood, tissues)
- Sample collection frequency and length

Follow Good Laboratory Practices (GLPs)
40 CFR 792

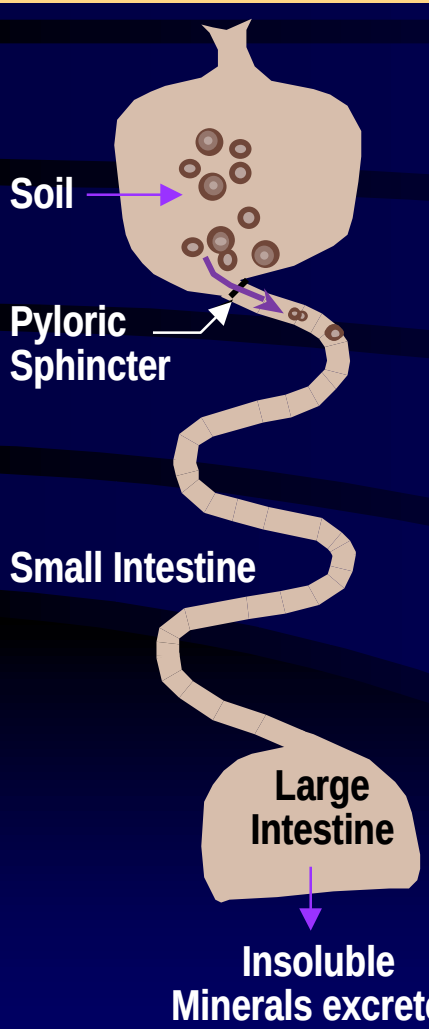
In Vitro Test System



Basis for Design of In Vitro Test System

- Form and solubility of metal will control bioavailability
- Uses design of test for Fe
- Uses human pediatric GI parameters
- Mimics fasting conditions

Gastro-Geochemistry of Metals



- pH of 1.8 (fasting) – 4 (fed)
- Some metal minerals dissolved
- Metals desorb
- pH increases to 7
- Metals precipitate/adsorb
- Soluble metals absorbed into bloodstream

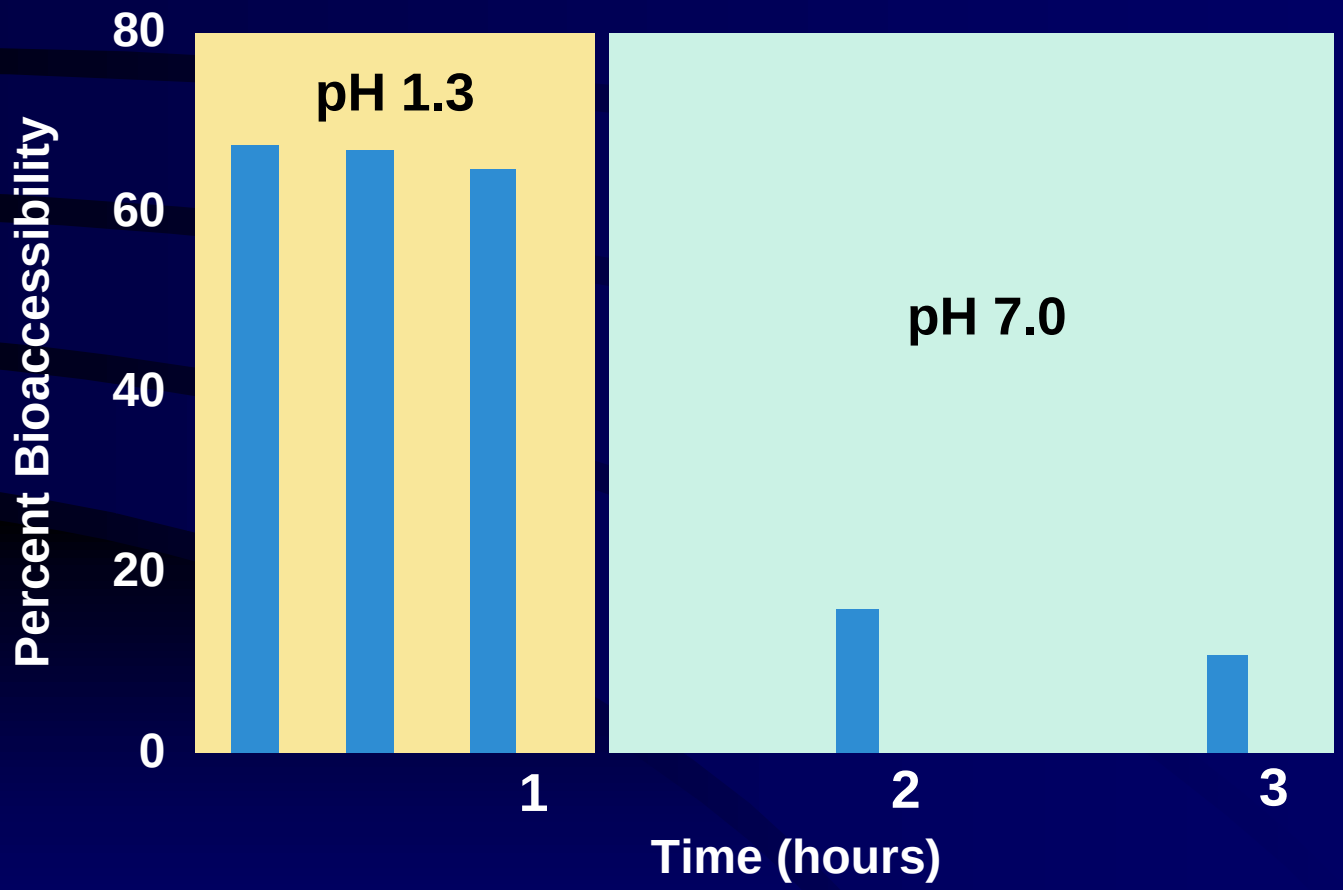
In Vitro Extraction: Stomach Phase

- Stomach solution – pH 1.5 HCl, organic acids
- Add 1.5 g soil (<250-micron size fraction) to 150 mL stomach fluid in reaction vessel
- 1 hour stirred incubation
- Collect 5-mL samples at 30 and 60 minutes and filter (0.45 micron) for metals analysis

In Vitro Extraction: Intestinal Phase

- Titrate to pH 7.0 with $NaHCO_3$
- Add bile salts and pancreatin
- Collect samples at 1 and 3 hours after pH 7 is attained, and filter (0.45 micron) for metals analysis

Bioaccessibility of Lead (pH 1.3)
Bartlesville Soil



Critical Design Factors for In Vitro Method

- **Chemistry:** pH = 1.5 or 2.5, fluid composition-buffers
- **Temperature:** 37°C water bath
- **Transit times:** incubation for 1 hour
- **Particle size:** selected < 250 microns
- **Mixing rate:** high rate of agitation

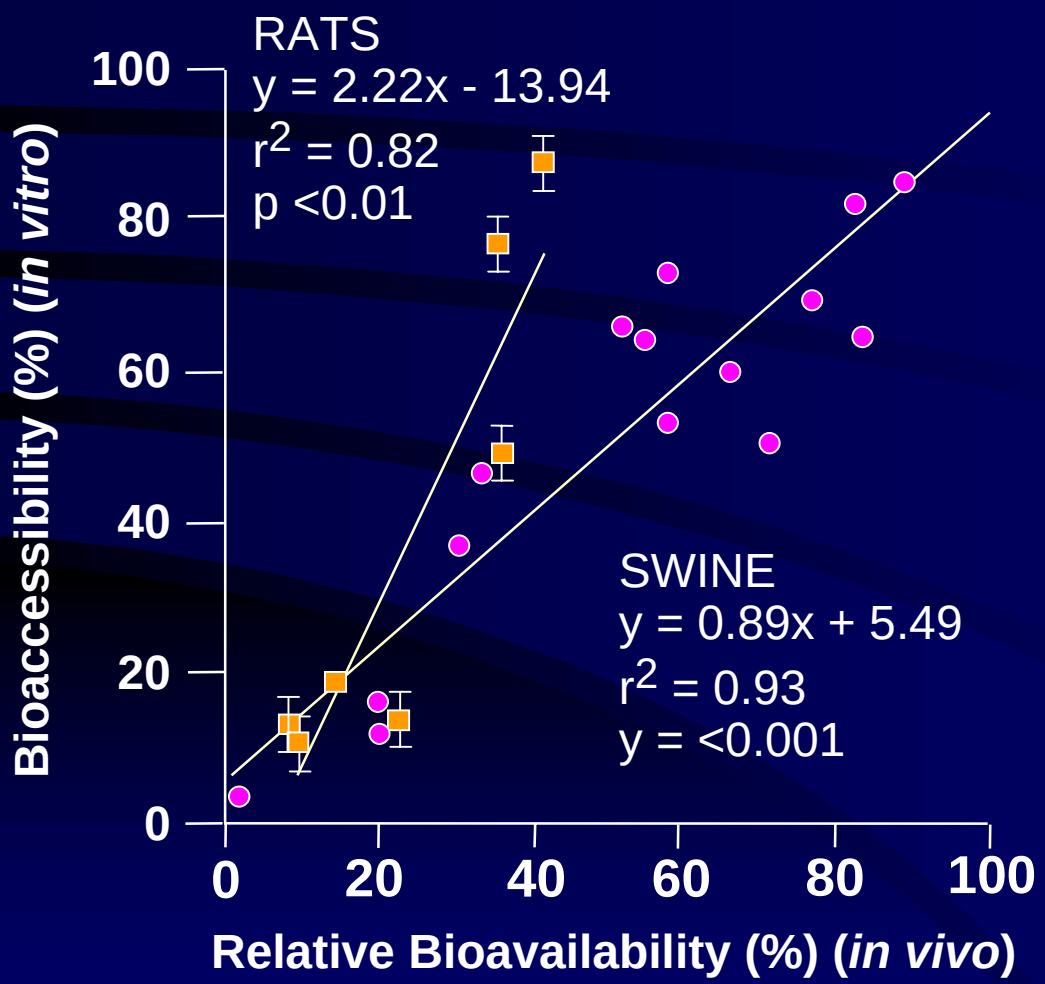
In Vitro Test Design Goals

- Accurately mimic key processes/chemistry
- Soluble vs. particulate uptake (0.45-micron filter)
- Predictive of nonequilibrium system
- Simple and reproducible
- Validation against in vivo studies

Validation of In Vitro Test System

- Mechanistic
- Correlational
- Combined mechanistic/correlational

In Vitro to In Vivo Correlation for Lead in Soil



Indicates upper and lower 95% confidence interval on *in vitro* measurements (n=6)

In Vitro Test Applications

- Estimate site-specific RAF
- Screen site materials
- Evaluate different substrates
- Evaluate amendment effects
- Investigate GI tract parameters

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- Definitions and review of risk assessment procedures
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- Geochemical considerations
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- Case studies
- Ecological risk assessment applications
- Conclusions: Role of RPM, resources, Navy policy recommendations

- Case studies

Case Studies

- Anaconda, MT — Arsenic
- Bartlesville, OK — Cadmium, Lead, Arsenic

Case Study: Anaconda, MT
Former Copper Smelter

Anaconda: Site Characteristics

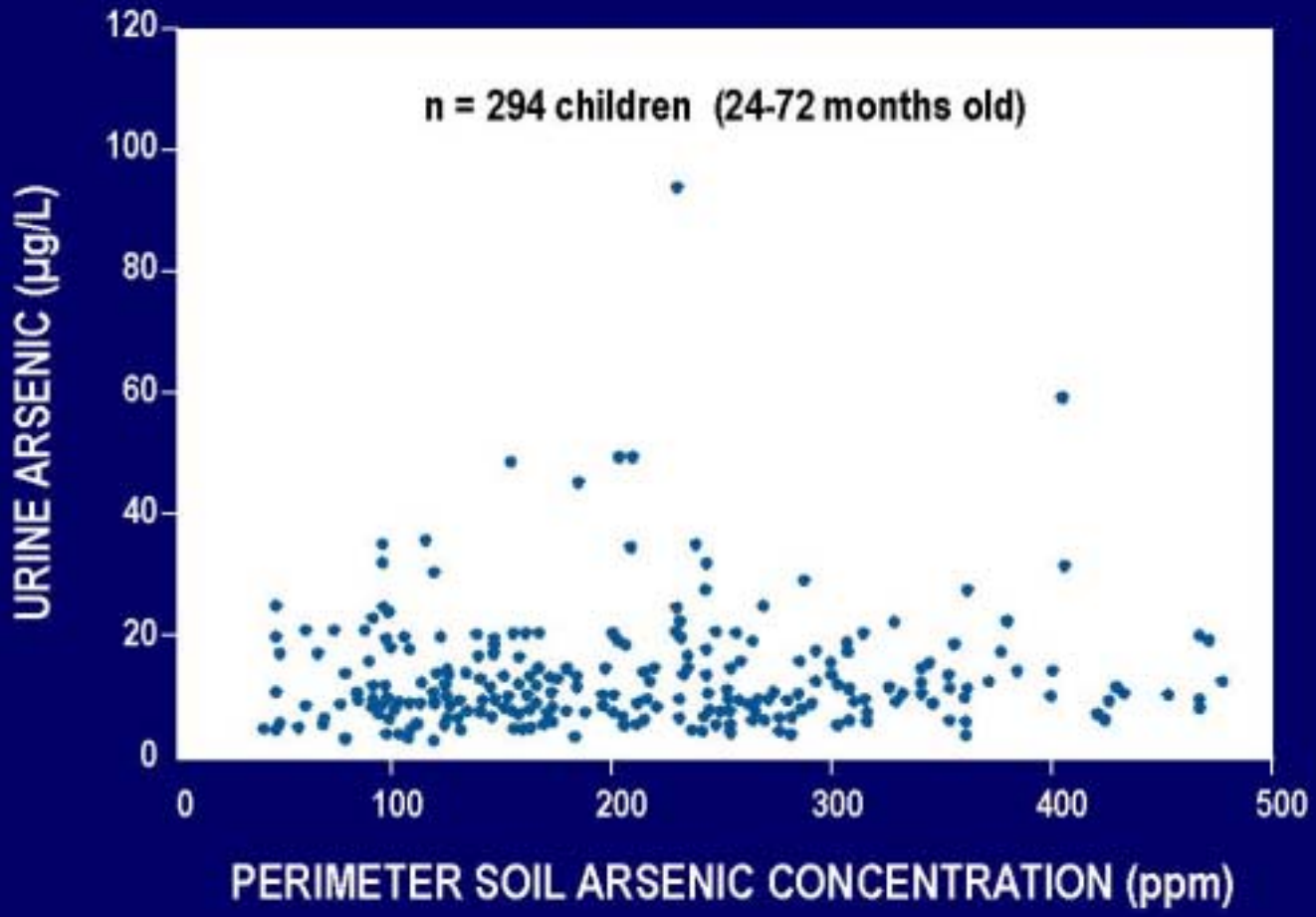
- 100 years of copper smelting
- ARCO bought Anaconda Minerals Company in the early 1970s
- HHRA focused on arsenic in soil
- Tens of square miles affected
- Average soil arsenic in town = 180 ppm

Anaconda: Critical Factors Supporting Soil Arsenic Cleanup Levels

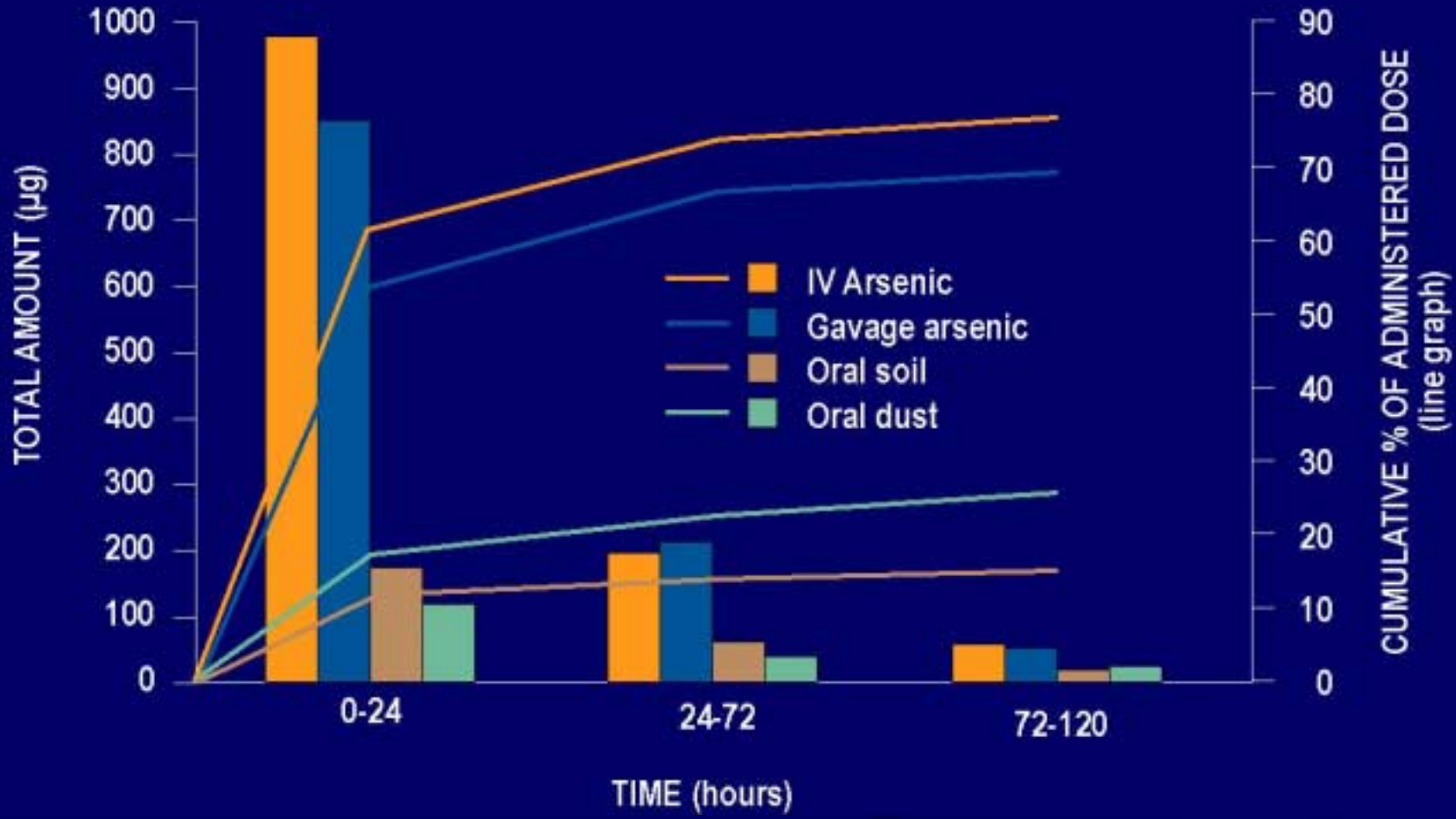
- Target risks close to $1x10^{-4}$
- Comprehensive exposure study
- Bioavailability study
- Indoor dust data
- Monte Carlo analysis

Relationship of Urine Arsenic to Arsenic Exposures

Anaconda Arsenic Exposure Study



Monkey Bioavailability Study: Arsenic Excretion in Urine



Anaconda: HHRA

- Arsenic RAF assumed to be 0.18 for soil, 0.25 for indoor dust
- Indoor dust concentration = 0.7 soil concentration
- $1x10^{-4}$ risk level ¡ 300 ppm (vs. default of 40 ppm)

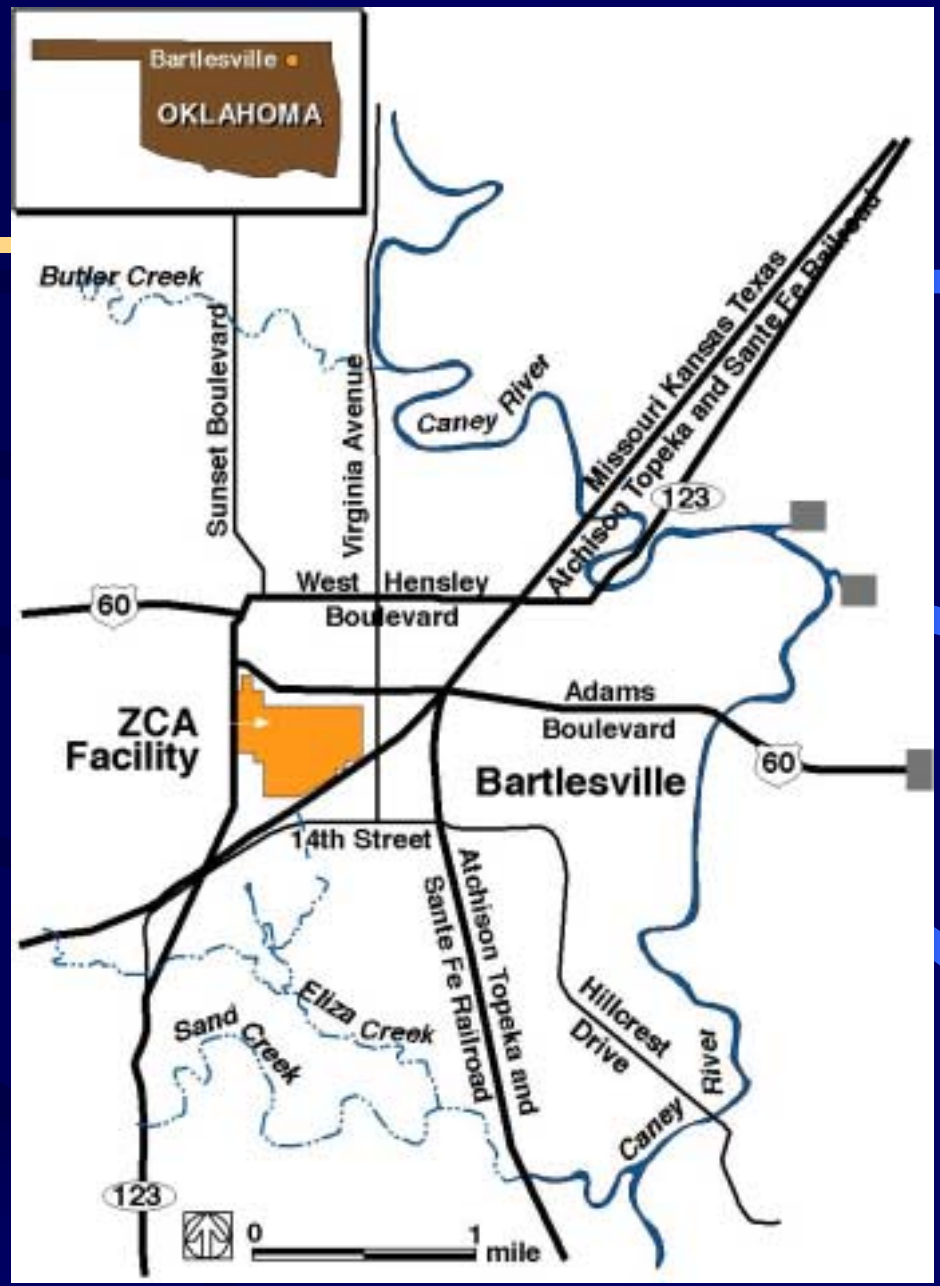
Anaconda: Arsenic Soil Cleanup Levels (ppm)

- Residential (ROD 9/96): 250
- Occupational (ROD 3/94): 500
- Recreational (ROD 3/94): 1,000

Anaconda: Reasons for Success

- Magnitude of site required site-specific solution
- EPA and ARCO RPMs worked closely
- EPA and ARCO toxicologists shared study plans and data
- Comprehensive exposure study supported bioavailability study

Case Study: Bartlesville Zinc Smelter



Bartlesville: Site Characteristics

- Former zinc smelter site
- PRP group: Cyprus Amax, Salomon, City
- Site investigation transferred from EPA to State (ODEQ)
- Superfund accelerated mode
  - Completed in 6 months
- Bioavailability study protocols included in work plan

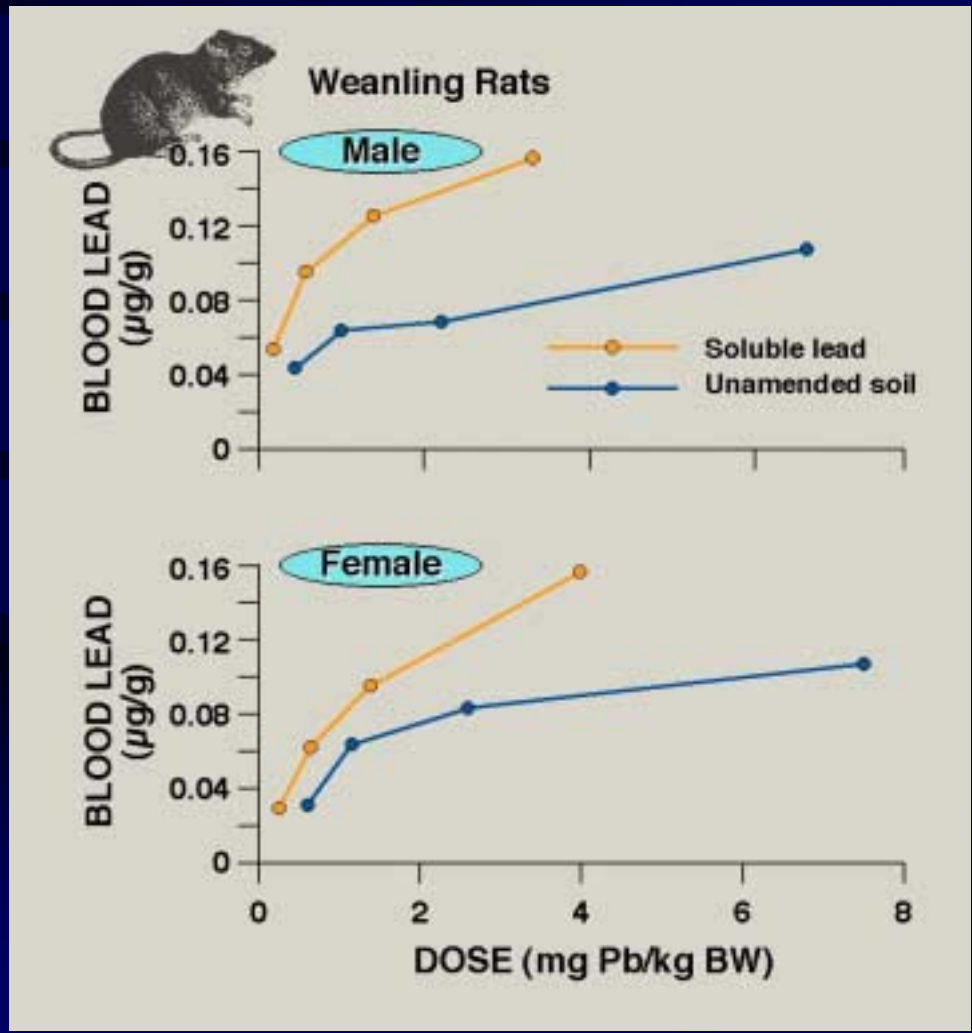
Chemicals of Potential Concern

- Lead – Childhood exposures (neurotoxicity)
  – Adult exposures (protection of fetus)
- Cadmium – Lifetime exposures (kidney toxicity)
- Arsenic – Lifetime exposures (cancer)

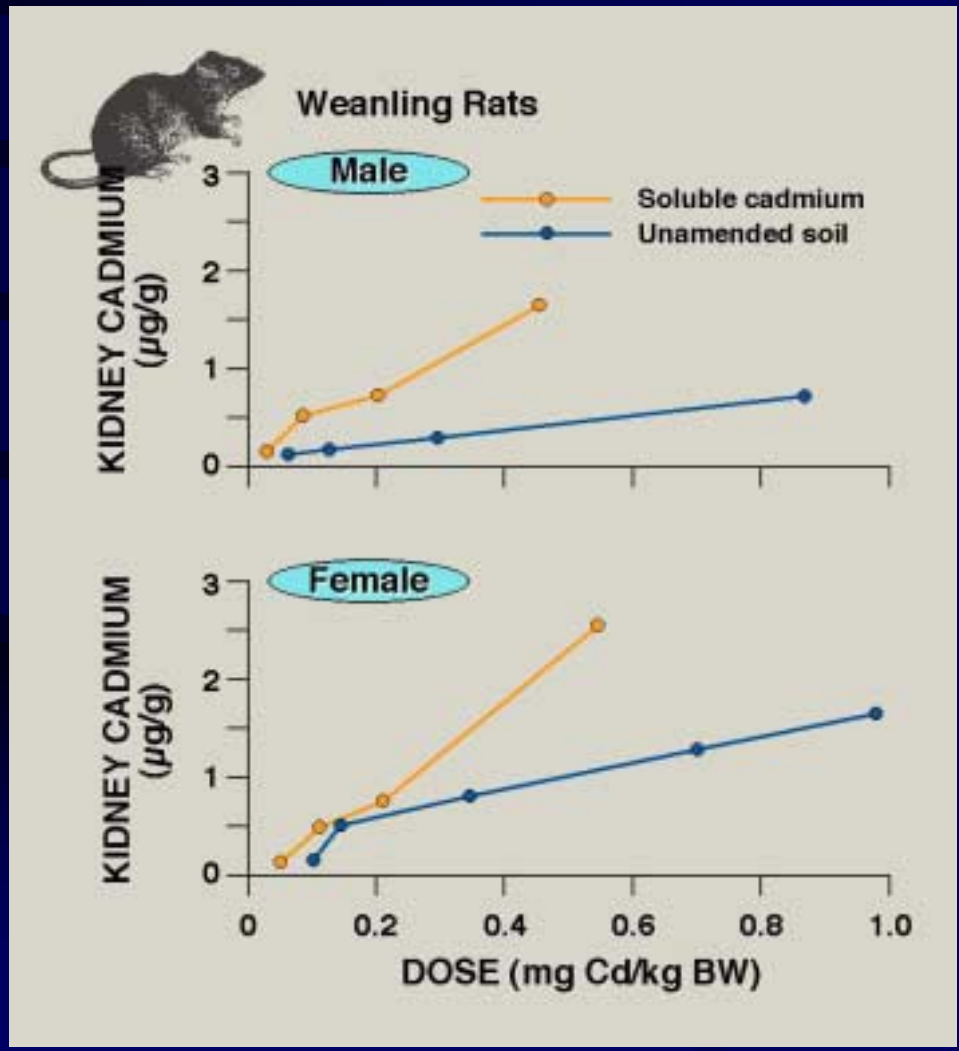
Bartlesville: Critical Studies to Support Risk-Based Remediation Goals

- Speciation analyses for lead, cadmium, and arsenic
- Bioavailability study of lead and cadmium in rats
- In vitro bioaccessibility study of arsenic

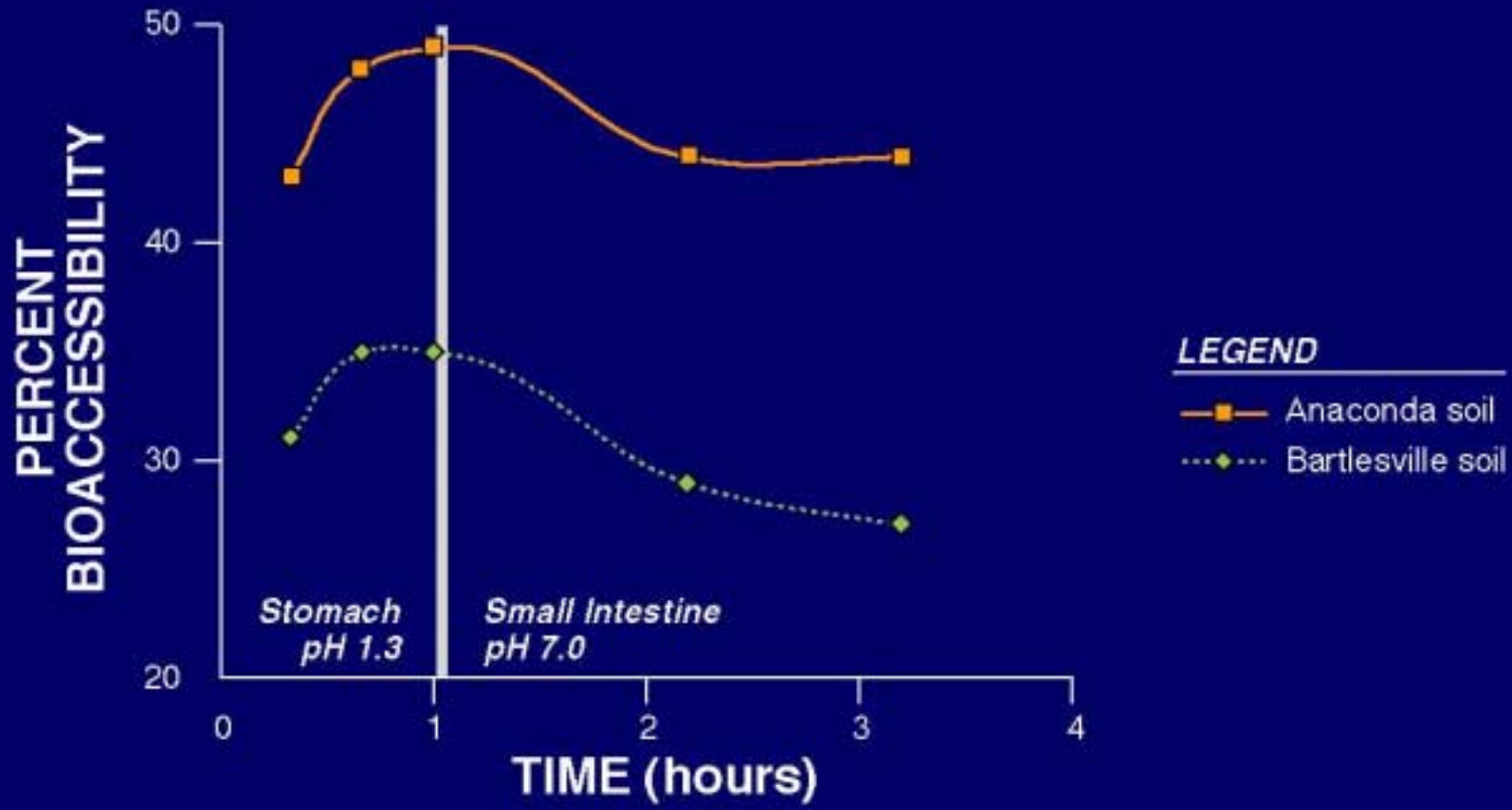
Bartlesville: Bioavailability of Lead in Soil



Bartlesville: Bioavailability of Cadmium in Soil



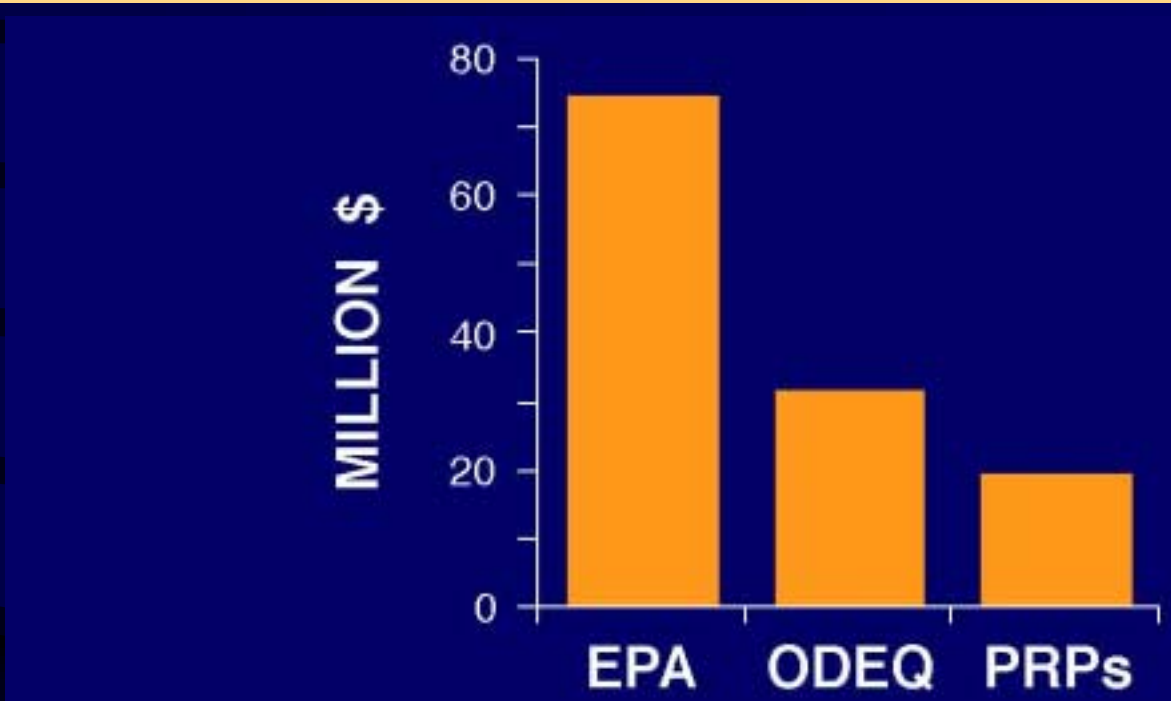
Arsenic Bioaccessibility



Bartlesville: Relative Bioavailability Impacts on Cleanup Levels

	Default	Relative Bioavailability	Approximate Change in Cleanup Levels
Lead	0.60	0.40	2x
Cadmium	1.0	0.33	3x
Arsenic	1.0	0.25	4x

Bartlesville: Residential Cleanup Levels[a] vs. Remediation Cost[b]



Cleanup Levels (mg/kg)	EPA	ODEQ	PRPs
Lead	500	925	925
Cadmium	30	100	190
Arsenic	20	60	88

[a] EPA PRGs, PRP values in RI report, ODEQ values in ROD 12/94

[b] Removal and off-site disposal

Bartlesville: Reasons for Success

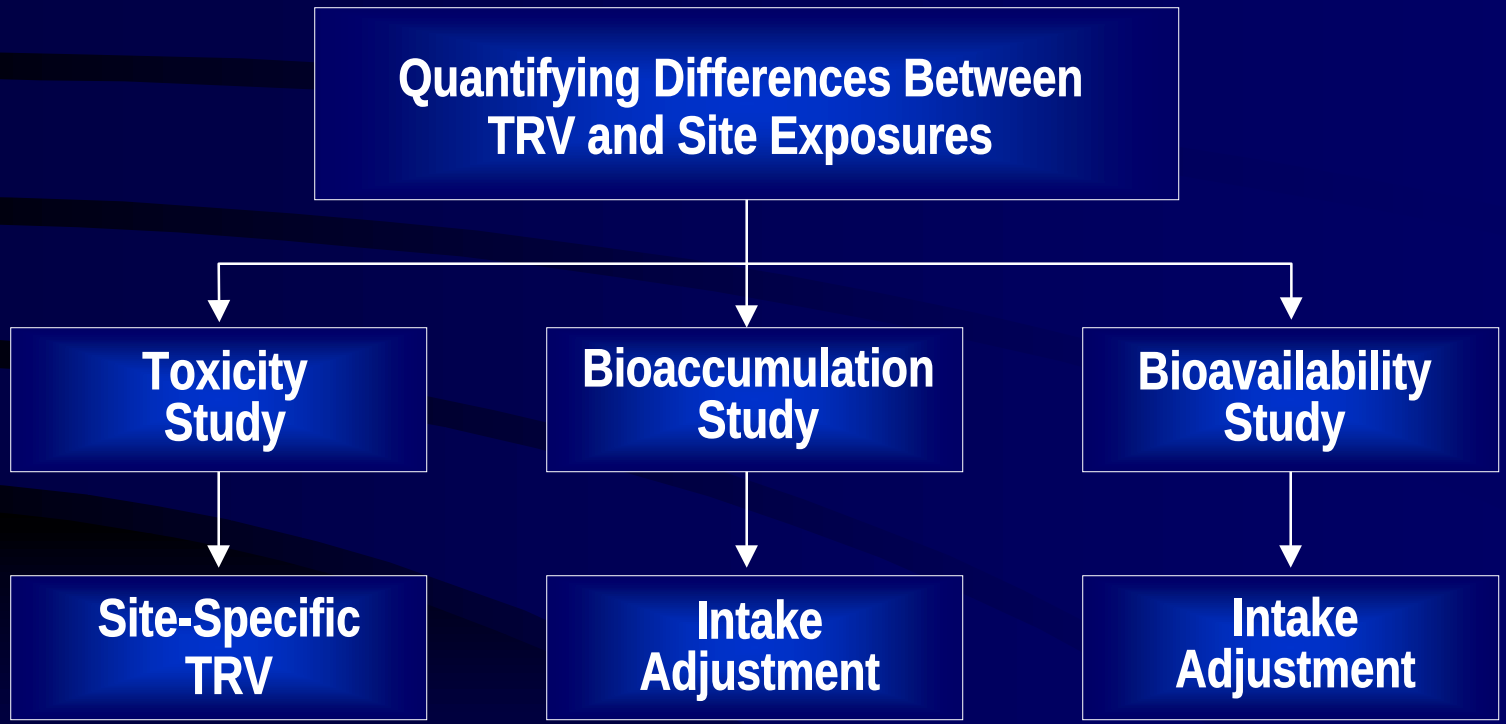
- Bioavailability studies proposed in work plan
- All critical stakeholders had toxicologists participating
- Stakeholders reviewed study protocols
- Stakeholders participated in data interpretation
- Protocols and results were peer reviewed
- Consistent results were obtained in supporting studies

Outline

- Definitions and review of risk assessment procedures
- Regulatory policies and precedents
- Geochemical considerations
- Methods review
- Case studies
- Ecological risk assessment applications
- Conclusions: Role of RPM, resources, Navy policy recommendations

- Ecological risk assessment applications

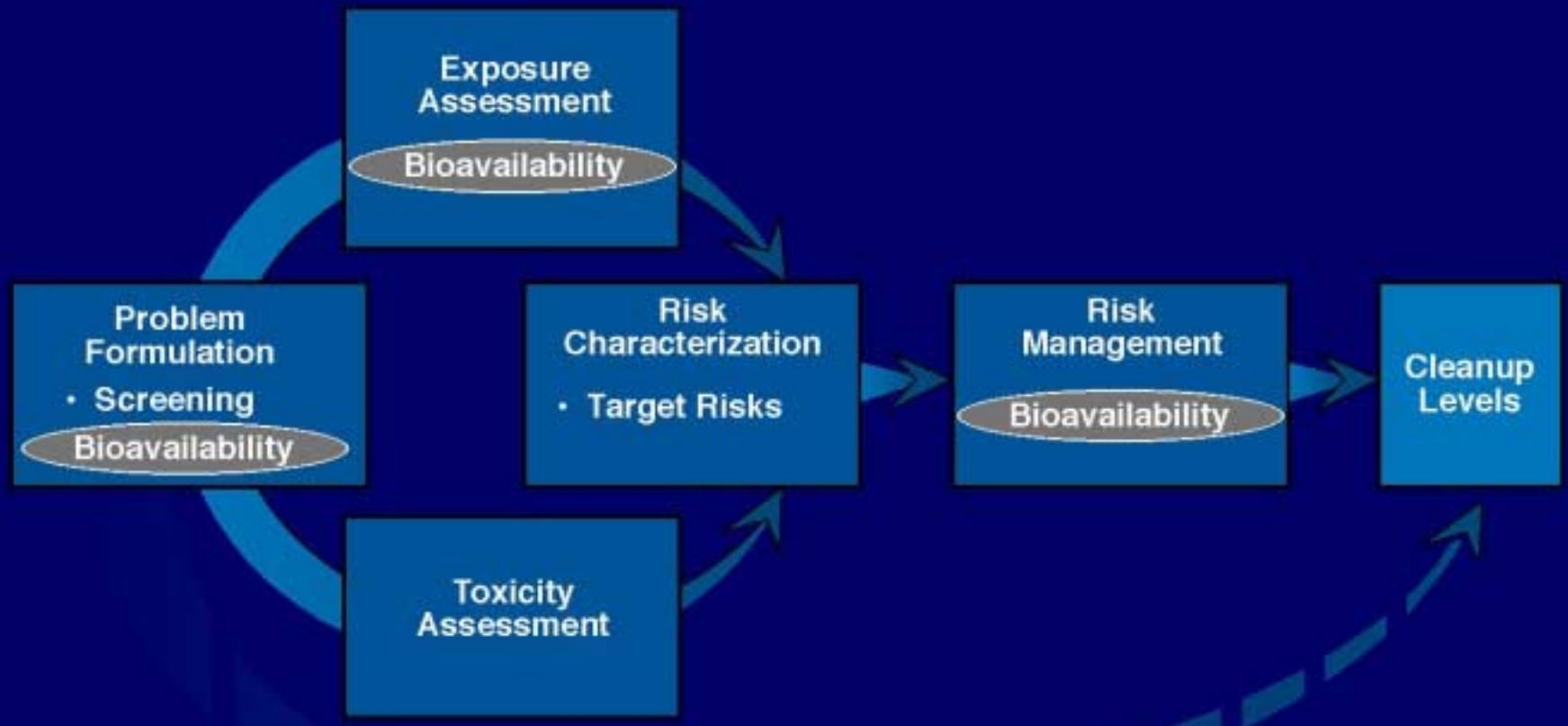
Bioavailability in ERA: Terrestrial Animals



What Does It Take to Get a Bioavailability Adjustment Accepted?

- Talk with stakeholders (identify need for more accurate risk assessment)
- Plan for adequate time and budgets
- Ensure adequate technical support
- Have study design critiqued
- Share data
- Obtain peer review
- Publish results

Applying Bioavailability Adjustments



Outline

- Definitions and review of risk assessment procedures
- Regulatory policies and precedents
- Geochemical considerations
- Methods review
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- Conclusions: Role of RPM, resources, Navy policy recommendations

- Conclusions

Policy Issues for the Navy to Consider

- Standard policy to identify the default assumption that RAF = 1.0
- Standard policy to address bioavailability in uncertainty analysis
- Management support for studies if cost-benefit evaluation is positive

References

- National Environmental Policy Institute. 1998. *Bioavailability: Implications for Science/CleanupPolicy.* Bioavailability Policy Project. White Paper.
- Battelle and Exponent. 1999. Draft Final Guide for Incorporating Bioavailability Adjustments into Human Health and Ecological Assessments at U.S. Navy and Marine Corps Facilities. Part 1: Overview of Metals Bioavailability. Prepared for NFESC, Port Hueneme, CA.
- U.S. Environmental Protection Agency. 1989. *Risk Assessment Guidance for Superfund, Volume 1: Human Health Evaluation Manual (Part A, Baseline Risk Assessment)*. EPA/540/1-89/002. Office of Emergency and Remedial Response, Washington, DC.

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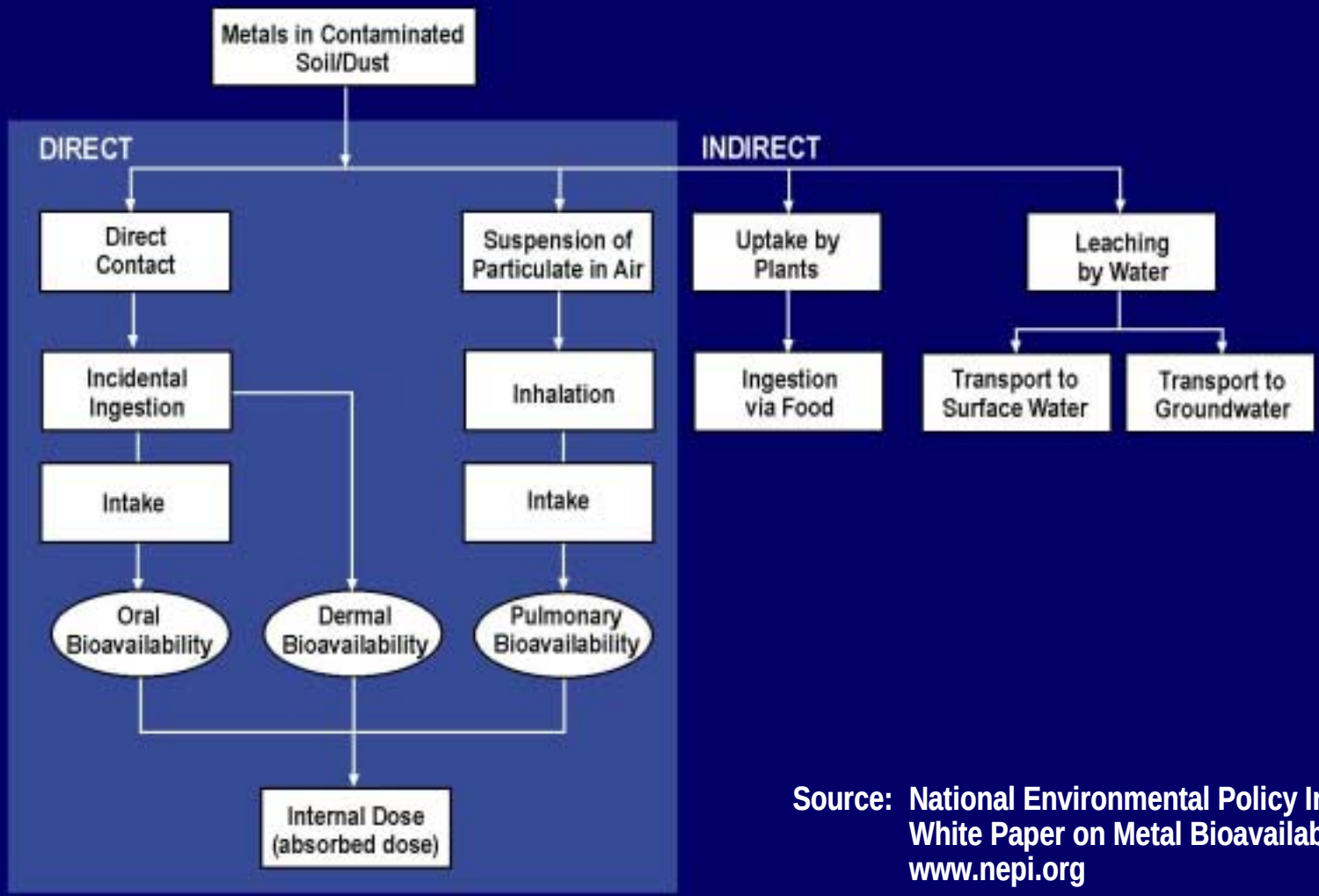
Or

- Your Local TSR

Why Were Bioavailability Adjustments Accepted at These Sites?

- Perceived need for more accurate risk assessments
- Involvement of qualified toxicologists for all critical stakeholders
- Stakeholder participation in study design (i.e., protocol development)
- Stakeholder participation in data interpretation
- Peer review of protocols and results
- Consistent results in supporting studies

Exposure Pathways for Metals in Soil/Dust: Direct Contact vs. Indirect Pathways



Source: National Environmental Policy Institute White Paper on Metal Bioavailability, www.nepi.org